CENTER FOR DRUG EVALUATION AND RESEARCH

Application Number 21-687

ADMINISTRATIVE DOCUMENTS
CORRESPONDENCE

Patent and Exclusivity Search Results from query on Appl No 019766 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
019766	001	4444784	DEC 23,2005			U-59
019766	001	4444784*PED	JUN 23,2006			U-59
019766	001	RE36481	JUL 10,2007			U-300
019766	001	RE36481*PED	JAN 10,2008			U-300
019766	001	RE36520	MAY 26,2009			U-300
019766	001	RE36520*PED	NOV 26,2009			U-300

7 method of tmt

} indication

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
019766	001	I-390	APR 16,2006
019766	001	I-350	OCT 18,2005
019766	001	PED	APR 18,2006

> 2 indications

Peds exclusivity

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(c)(3)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**

EZETIMIBE 10 mg

Patent and Exclusivity Search Results from query on Appl No 021445 Product 001 in the OB_Rx list.

Patent Data

Appl No	Prod No	Patent No	Patent Expiration	Drug Substance Claim	Drug Product Claim	Patent Use Code
021445	001	5846966	SEP 21,2013			U-474
021445	001	RE37721	JUN 16,2015			U-473

> for indication
↓ plasma cholesterol levels

Exclusivity Data

Appl No	Prod No	Exclusivity Code	Exclusivity Expiration
021445	001	NCE	OCT 25,2007

new chemical entity

Additional information:
1. Patents are published upon receipt by the Orange Book Staff and may not reflect the official receipt date as described in 21 CFR 314.53(c)(3)(5).
2. Patents submitted on FDA Form 3542 and listed after August 18, 2003 will have one to three patent codes indicating specific patent claims as submitted by the sponsor and are detailed in the above table.
3. Patents listed prior to August 18, 2003 are flagged with method of use claims only as applicable and submitted by the sponsor. These patents may not be flagged with respect to other claims which may apply.
4. *PED and PED represent pediatric exclusivity. Patents with pediatric exclusivity granted after August 18, 2003 will be indicated with *PED as was done prior to August 18, 2003. Patents with *PED added after August 18, 2003 will not contain any information relative to the patent itself other than the *PED extension. Information related specifically to the patent will be conveyed on the original patent only.

View a list of all patent use codes
View a list of all exclusivity codes

Return to Electronic Orange Book Home Page

FDA/Center for Drug Evaluation and Research
Office of Generic Drugs
Division of Labeling and Program Support
Update Frequency:
Orange Book Data - **Monthly**
Orange Book Data Updated Through May, 2004
Orange Book Patent Data Only - **Daily**
Patent Data Last Updated: July 13, 2004

Department of Health and Human Services
Food and Drug Administration

Form Approved: OMB No. 0910-0513
Expiration Date: 07/31/06

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

NDA NUMBER
To be assigned

NAME OF APPLICANT / NDA HOLDER
MSP Singapore Co., LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
VYTORIN (ezetimibe/simvastatin) Tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Ezetimibe Simvastatin	Ezetimibe/Simvastatin: 10mg/10mg; 10 mg/20 mg; 10mg/40mg; and 10 mg/80 mg.

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4). Within thirty (30) days after approval of an NDA or supplement, or within thirty (30) days of issuance of a new patent, a new patent declaration must be submitted pursuant to 21 CFR 314.53(c)(2)(ii) with all of the required information based on the approved NDA or supplement. The information submitted in the declaration form submitted upon or after approval will be the *only* information relied upon by the FDA for listing a patent in the Orange Book.

For hand-written or typewriter versions (only) of this report: If additional space is required for any narrative answer (i.e., one that does not require a "Yes" or "No" response), please attach an additional page referencing the question number.

FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment or supplement, complete above section and sections 5 and 6.

1. GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
4,444,784	4/24/1984	12/23/2005

d. Name of Patent Owner	Address *(of Patent Owner)*	
	P. O. Box HM 1429	
	City/State	
	Hamilton HM FX Bermuda	
MSD Technology, L. P.	ZIP Code not applicable	FAX Number *(if available)*
	Telephone Number 441-294-1556	E-Mail Address *(if available)*

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3)and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)	Address *(of agent or representative named in 1.e.)*	
	One Merck Drive, P. O. Box 1000	
	City/State	
	Whitehouse Station, New Jersey	
	ZIP Code 08889-0100	FAX Number *(if available)* 908-735-1244
Office of General Counsel	Telephone Number 908-423-5259	E-Mail Address *(if available)* ken_frazier@merck.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above?	☐ Yes	☒ No
g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date?	☐ Yes	☐ No

6. Declaration Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner (*Attorney, Agent, Representative or other Authorized Official*) (*Provide Information below*)	Date Signed
	September 9, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Melvin Winokur, Patent Department, Merck & Co., Inc.	
Address 126 East Lincoln Ave., P.O. Box 2000	City/State Rahway, NJ
ZIP Code 07065-0907	Telephone Number (732) 594-7234
FAX Number *(if available)* (732) 594-4720	E-Mail Address *(if available)* mel_ winokur@merck.com

APPEARS THIS WAY
ON ORIGINAL

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2. Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3. Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4. Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Claim Number *(as listed in the patent)* 12	Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement? ☒ Yes ☐ No	

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: (*Submit indication or method of use information as identified specifically in the proposed labeling.*)

VYTORIN is indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

VYTORIN is indicated for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

5. No Relevant Patents

For this pending NDA, amendment or supplement, there are no relevant patents that claim the approved drug substance (active ingredient), drug product (formulation or composition) or methods(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use or sale of the drug product. ☐ Yes

Department of Health and Human Services
Food and Drug Administration

PATENT INFORMATION SUBMITTED WITH THE FILING OF AN NDA, AMENDMENT, OR SUPPLEMENT

For Each Patent That Claims a Drug Substance (Active Ingredient), Drug Product (Formulation and Composition) and/or Method of Use

Form Approved: OMB No. 0910-0513
Expiration Date: 7/31/06
See OMB Statement on Page 3.

NDA NUMBER
To Be Assigned

NAME OF APPLICANT / NDA HOLDER
MSP Singapore Company, LLC

The following is provided in accordance with Section 505(b) and (c) of the Federal Food, Drug, and Cosmetic Act.

TRADE NAME (OR PROPOSED TRADE NAME)
VYTORIN™ (ezetimibe/simvastatin) Tablets

ACTIVE INGREDIENT(S)	STRENGTH(S)
Ezetimibe Simvastatin	Ezetimibe/simvastatin 10mg/10mg;10mg/20mg; 10mg/40mg; and 10mg/80mg.

DOSAGE FORM
Tablets

This patent declaration form is required to be submitted to the Food and Drug Administration (FDA) with an NDA application, amendment, or supplement as required by 21 CFR 314.53 at the address provided in 21 CFR 314.53(d)(4).
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FDA will not list patent information if you submit an incomplete patent declaration or the patent declaration indicates the patent is not eligible for listing.

For each patent submitted for the pending NDA, amendment, or supplement referenced above, you must submit all the information described below. If you are not submitting any patents for this pending NDA, amendment, or supplement, complete above section and sections 5 and 6.

1 - GENERAL

a. United States Patent Number	b. Issue Date of Patent	c. Expiration Date of Patent
RE 37,721	5/28/2002	6/16/2015

d. Name of Patent Owner
SCHERING CORPORATION

Address *(of Patent Owner)*
2000 Galloping Hill Road

City/State
Kenilworth, New Jersey

ZIP Code	FAX Number *(if available)*
07033-0530	(908)298-5388
Telephone Number	**E-Mail Address *(if available)***
(908)298-5037	thomas.hoffman@spcorp.com

e. Name of agent or representative who resides or maintains a place of business within the United States authorized to receive notice of patent certification under section 505(b)(3) and (j)(2)(B) of the Federal Food, Drug, and Cosmetic Act and 21 CFR 314.52 and 314.95 (if patent owner or NDA applicant/holder does not reside or have a place of business within the United States)

☞ Thomas D. Hoffman

Address *(of agent or representative named in 1.e.)*
SCHERING CORPORATION- Patent Dept. K-6-1-1990
2000 Galloping Hill Road

City/State
Kenilworth, New Jersey

ZIP Code	FAX Number *(if available)*
07033-0530	(908)298-5388
Telephone Number	**E-Mail Address *(if available)***
(908)298-5037	thomas.hoffman@spcorp.com

f. Is the patent referenced above a patent that has been submitted previously for the approved NDA or supplement referenced above? ☐ Yes ☒ No

g. If the patent referenced above has been submitted previously for listing, is the expiration date a new expiration date? ☐ Yes ☒ No

6. Declaration/Certification

6.1 ***The undersigned declares that this is an accurate and complete submission of patent information for the NDA, amendment, or supplement pending under section 505 of the Federal Food, Drug, and Cosmetic Act. This time-sensitive patent information is submitted pursuant to 21 CFR 314.53. I attest that I am familiar with 21 CFR 314.53 and this submission complies with the requirements of the regulation. I verify under penalty of perjury that the foregoing is true and correct.***

Warning: A willfully and knowingly false statement is a criminal offense under 18 U.S.C. 1001.

6.2 Authorized Signature of NDA Applicant/Holder or Patent Owner *(Attorney, Agent, Representative or other Authorized Official) (Provide Information below)*	Date Signed
Thomas D. Hoffman	September 9, 2003

NOTE: Only an NDA applicant/holder may submit this declaration directly to the FDA. A patent owner who is not the NDA applicant/holder is authorized to sign the declaration but may not submit it directly to FDA. 21 CFR 314.53(c)(4) and (d)(4).

Check applicable box and provide information below.

☐ NDA Applicant/Holder	☐ NDA Applicant's/Holder's Attorney, Agent (Representative) or other Authorized Official
☐ Patent Owner	☒ Patent Owner's Attorney, Agent (Representative) or Other Authorized Official

Name Thomas D. Hoffman	
Address SCHERING CORPORATION Patent Dept., K-6-1-1990 2000 Galloping Hill Road	City/State Kenilworth, New Jersey
ZIP Code 07033	Telephone Number (908)298-5037
FAX Number *(if available)* (908)298-5388	E-Mail Address *(if available)* thomas.hoffman@spcorp.com

For the patent referenced above, provide the following information on the drug substance, drug product and/or method of use that is the subject of the pending NDA, amendment, or supplement.

2 Drug Substance (Active Ingredient)

2.1 Does the patent claim the drug substance that is the active ingredient in the drug product described in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
2.2 Does the patent claim a drug substance that is a different polymorph of the active ingredient described in the pending NDA, amendment, or supplement?	☐ Yes	☒ No
2.3 If the answer to question **2.2** is "Yes," do you certify that, as of the date of this declaration, you have test data demonstrating that a drug product containing the polymorph will perform the same as the drug product described in the NDA? The type of test data required is described at 21 CFR 314.53(b).	☐ Yes	☐ No
2.4 Specify the polymorphic form(s) claimed by the patent for which you have the test results described in **2.3**.		
2.5 Does the patent claim only a metabolite of the active ingredient pending in the NDA or supplement? (Complete the information in section 4 below if the patent claims a pending method of using the pending drug product to administer the metabolite.)	☐ Yes	☒ No
2.6 Does the patent claim only an intermediate?	☐ Yes	☒ No
2.7 If the patent referenced in **2.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

3 Drug Product (Composition/Formulation)

3.1 Does the patent claim the drug product, as defined in 21 CFR 314.3, in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
3.2 Does the patent claim only an intermediate?	☐ Yes	☒ No
3.3 If the patent referenced in **3.1** is a product-by-process patent, is the product claimed in the patent novel? (An answer is required only if the patent is a product-by-process patent.)	☐ Yes	☐ No

4 Method of Use

Sponsors must submit the information in section 4 separately for each patent claim claiming a method of using the pending drug product for which approval is being sought. For each method of use claim referenced, provide the following information:

4.1 Does the patent claim one or more methods of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No
4.2 Claim Number (*as listed in the patent*): 13 — Does the patent claim referenced in **4.2** claim a pending method of use for which approval is being sought in the pending NDA, amendment, or supplement?	☒ Yes	☐ No

4.2a If the answer to **4.2** is "Yes," identify with specificity the use with reference to the proposed labeling for the drug product.

Use: *(Submit indication or method of use information as identified specifically in the proposed labeling.)*

VYTORIN is indicated (1)as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo B, TG, and non-HDL-C,and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia;(2) for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or if such treatments are unavailable.

5 No Relevant Patents

For this pending NDA, amendment, or supplement, there are no relevant patents that claim the drug substance (active ingredient), drug product (formulation or composition) or method(s) of use, for which the applicant is seeking approval and with respect to which a claim of patent infringement could reasonably be asserted if a person not licensed by the owner of the patent engaged in the manufacture, use, or sale of the drug product.	☐ Yes

EXCLUSIVITY SUMMARY FOR NDA # 21-687_____ SUPPL #_____

Trade Name _Vytorin_
Generic Name ezetimibe/simvastatin tablets [10/10, 10/20, 10/40, 10/80]

Applicant Name MSP Singapore Company

Approval Date If Known ___July 23, 2004____

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following question about the submission.

a) It a 505(b)(1), 505(b)(2) or efficacy supplement?
YES /_X_/ NO /___/

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1)_____

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES /_/ NO /X_/

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

Note: A bioequivalence study was required for approval.

If it is a **supplement** requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:
_____N/A_____

_____

d) Did the applicant request exclusivity?

YES /___/ NO /_X_/

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

_____N/A_____

e) Has pediatric exclusivity been granted for this Active Moiety?

YES /_X_/ NO /__/

Note: simvastatin, yes ; ezetimibe,no

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Writen Request?

_____NO_____

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES /___/ NO /_X/

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

N/A

If "yes," identify the approved drug product(s) containing the

active moiety, and, if known, the NDA #(s).

N/A

NDA# _____ _____

NDA# _____ _____

NDA# _____ _____

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES /_X_/ NO /___/

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA# __21-445_ _____

NDA# __19-766__ _____

NDA# _____ _____

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.) IF "YES" GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDA'S AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations"

to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES /X/ NO /___/

Note: Protocol no. P005 and P038, 2 new studies Primary Hypercholesterolemia

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES /__/ NO /_X_/

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

Bioequivalence study was the only study needed for approval, the clinical studies mentioned in item #1 above, were for modification of the package insert, but were not required for approval.

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES /___/ NO /_X_/

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES /___/ NO /___/

If yes, explain:

N/A

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES /___/ NO /X/

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

None

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

NOT APPLICABLE

Investigation #1 YES /__/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

_____ _____

_____ _____

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES /_/ NO /___/

Investigation #2 YES /___/ NO /___/

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

_____ _____

_____ _____

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"): N/A

_____ _____

_____ _____

4. To be eligible for exclusivity, a new investigation that is essential to approval must also have been conducted or sponsored by

the applicant. An investigation was "conducted or sponsored by" the applicant if, before or during the conduct of the investigation, 1) the applicant was the sponsor of the IND named in the form FDA 1571 filed with the Agency, or 2) the applicant (or its predecessor in interest) provided substantial support for the study. Ordinarily, substantial support will mean providing 50 percent or more of the cost of the study.

NOT APPLICABLE

a) For each investigation identified in response to question 3(c): if the investigation was carried out under an IND, was the applicant identified on the FDA 1571 as the sponsor?

Investigation #1

IND # _____ YES /__/ NO /___/ Explain: _____

Investigation #2

IND # _____ YES /__/ NO /___/ Explain: _____

(b) For each investigation not carried out under an IND or for which the applicant was not identified as the sponsor, did the applicant certify that it or the applicant's predecessor in interest provided substantial support for the study? N/A

Investigation #1

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

Investigation #2

YES /___/ Explain _____ NO /___/ Explain _____

_____ _____

_____ _____

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be

considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES /___/ NO /_X__/

If yes, explain: _____

_____

Signature Monika Johnson, PharmD Date August 3, 2004
Title: Project Manager

Signature of Date: August 3, 2004
Division Director
David G. Orloff, MD

Form OGD-011347 Revised 05/10/2004

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/s/

Mary Parks
8/3/04 04:28:01 PM
for Dr. Orloff

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PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

NDA/BLA # : 21-687 **Supplement Type (e.g. SE5):** _____ **Supplement Number:**

tamp Date: September 24, 2003 **Action Date:** July 23, 2004

HFD 510 **Trade and generic names/dosage form:** Vytorin (ezetimibe/simvastatin) 10/10, 10/20, 10/40 amd 10/80 mg tablets

Applicant: MSP Singapore Company, LLC **Therapeutic Class:** Lipid altering agent

Indication(s) previously approved: None for Vytorin

Each approved indication must have pediatric studies: Completed, Deferred, and/or Waived.

Number of indications for this application(s): 2

Indication #1: as adjunctive therapy to diet, to reduce elevated total-C, LDL-C, Apo B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia

Is there a full waiver for this indication (check one)?

Yes: Please proceed to Section A.

X No: Please check all that apply: x **Partial Waiver (0-9yrs)** x **Deferred (10-16 yrs)** ____ **Completed**

NOTE: More than one may apply

Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:** _____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min	**kg**	**mo.** 0	**yr.**	**Tanner Stage**
Max	**kg**	**mo.**	**yr.** 9	**Tanner Stage**

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**

- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- **X Other:** **Disease/condition not clinically significant in this age group.**

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min ____	**kg**____	**mo.**____	**yr.** 10	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.** 16	**Tanner Stage**____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**

X Adult studies ready for approval **Note: WR for Zetia (NDA 21-445) for subgroup/indication, tmt herozygous familial hypercholesterolemia. No WR for remaining age group b/c of too few patients, may reconsider at a later date**

- ☐ **Formulation needed**

Other:_____

Date studies are due (mm/dd/yy): 7/31/09

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min ____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____
Max____	**kg**____	**mo.**____	**yr.**____	**Tanner Stage**____

Comments:

If there are additional indications, please proceed to Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____

Regulatory Project Manager

cc: **NDA**
HFD-960/ Grace Carmouze

(revised 12-22-03)

Attachment A

(This attachment is to be completed for those applications with multiple indications only.)

Indication #2: for the reduction of elevated total-C and LDL-C in patients with homozygous familial hypercholesterolemia, as an adjunct to other lipid-lowering treatments (e.g., LDL apheresis) or alone, if such treatments are unavailable.

Is there a full waiver for this indication (check one)?

X Yes: Please proceed to Section A.

☐ **No: Please check all that apply: ____Partial Waiver ____Deferred ____Completed**

NOTE: More than one may apply
Please proceed to Section B, Section C, and/or Section D and complete as necessary.

Section A: Fully Waived Studies

Reason(s) for full waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- **X Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Other:**_____

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please see Attachment A. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section B: Partially Waived Studies

Age/weight range being partially waived:

Min _____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____
Max_____	**kg**_____	**mo.**_____	**yr.**_____	**Tanner Stage**_____

Reason(s) for partial waiver:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

If studies are deferred, proceed to Section C. If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section C: Deferred Studies

Age/weight range being deferred:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Reason(s) for deferral:

- ☐ **Products in this class for this indication have been studied/labeled for pediatric population**
- ☐ **Disease/condition does not exist in children**
- ☐ **Too few children with disease to study**
- ☐ **There are safety concerns**
- ☐ **Adult studies ready for approval**
- ☐ **Formulation needed**
- ☐ **Other:**_____

Date studies are due (mm/dd/yy): _____

If studies are completed, proceed to Section D. Otherwise, this Pediatric Page is complete and should be entered into DFS.

Section D: Completed Studies

Age/weight range of completed studies:

Min _____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____
Max_____ **kg**_____ **mo.**_____ **yr.**_____ **Tanner Stage**_____

Comments:

If there are additional indications, please copy the fields above and complete pediatric information as directed. If there are no other indications, this Pediatric Page is complete and should be entered into DFS.

This page was completed by:

{See appended electronic signature page}

_____
Regulatory Project Manager

cc: **NDA 21-687**
HFD-960/ Grace Carmouze

(revised 10-14-03)

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/s/

Monika Johnson
8/3/04 04:38:48 PM

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Submit 9/24/03

Ezetimibe/Simvastatin Combination Tablet
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, MSP Singapore Company, LLC, a joint venture between Merck & Co., Inc. and Schering Corporation, did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Robert A. McMahon
Vice President and General Manager

9/24/2003
Date

Diane C. Louie, M.D., M.P.H.
Associate Director
Regulatory Affairs

9/24/2003
Date

APPEARS THIS WAY
ON ORIGINAL

Submission 1/23/04

Ezetimibe/Simvastatin Combination Tablet
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, MSP Singapore Company, LLC, a joint venture between Merck & Co., Inc. and Schering Corporation, did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Diane Louie, MD, MPH

Diane C. Louie, M.D., M.P.H.
Associate Director
Regulatory Affairs

January 23, 2004
Date

APPEARS THIS WAY
ON ORIGINAL

Ezetimibe/Simvastatin Combination Tablet
Item 16 - Debarment Certification

As required by §306(k)(1) of 21 U.S.C. 335a(k)(1), we hereby certify that, in connection with this application, MSP Singapore Company, LLC, a joint venture between Merck & Co., Inc. and Schering Corporation, did not and will not use in any capacity the services of any person debarred under subsections 306(a) or (b) of the Act.

Diane Louie MD MPH 9/24/03

Diane C. Louie, M.D., M.P.H.
Associate Director
Regulatory Affairs

Date

APPEARS THIS WAY
ON ORIGINAL

Submission 1/23/04

Ezetimibe/Simvastatin Combination Tablet
Financial Disclosure Information

Financial Disclosure Information

A. Introduction

In compliance with the U.S. Food and Drug Administration's regulation *Financial Disclosure by Clinical Investigators* published February 02, 1998 and revised December 31, 1998, the following item details the requested information concerning the financial interests of and compensation to investigators participating in the clinical studies presented in this application.

B. Discussion

Financial Disclosure information is not required with the supplemental marketing application as the clinical studies do not meet the definition of a "covered study" as defined by the regulation (21 CFR 54.2(e)).

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: 3/31/02

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☑ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Tables C-1 and C-2	
	Ezetimibe/Simvastatin Combination Tablet	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Melissa King	Controller, Merck Corporate Finance
FIRM/ORGANIZATION: Merck & Co., Inc.	
SIGNATURE: Melissa King	DATE: 9/3/03

Paperwork Reduction Act Statement

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number. Public reporting burden for this collection of information is estimated to average 1 hour per response, including time for reviewing instructions, searching existing data sources, gathering and maintaining the necessary data, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information to the address to the right:

Department of Health and Human Services
Food and Drug Administration
5600 Fishers Lane, Room 14C-03
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

CERTIFICATION: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006.

TO BE COMPLETED BY APPLICANT

With respect to all covered clinical studies (or specific clinical studies listed below (if appropriate)) submitted in support of this application, I certify to one of the statements below as appropriate. I understand that this certification is made in compliance with 21 CFR part 54 and that for the purposes of this statement, a clinical investigator includes the spouse and each dependent child of the investigator as defined in 21 CFR 54.2(d).

Please mark the applicable checkbox.

☒ (1) As the sponsor of the submitted studies, I certify that I have not entered into any financial arrangement with the listed clinical investigators (enter names of clinical investigators below or attach list of names to this form) whereby the value of compensation to the investigator could be affected by the outcome of the study as defined in 21 CFR 54.2(a). I also certify that each listed clinical investigator required to disclose to the sponsor whether the investigator had a proprietary interest in this product or a significant equity in the sponsor as defined in 21 CFR 54.2(b) did not disclose any such interests. I further certify that no listed investigator was the recipient of significant payments of other sorts as defined in 21 CFR 54.2(f).

Clinical Investigators		
	See Attached List	

☐ (2) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that based on information obtained from the sponsor or from participating clinical investigators, the listed clinical investigators (attach list of names to this form) did not participate in any financial arrangement with the sponsor of a covered study whereby the value of compensation to the investigator for conducting the study could be affected by the outcome of the study (as defined in 21 CFR 54.2(a)); had no proprietary interest in this product or significant equity interest in the sponsor of the covered study (as defined in 21 CFR 54.2(b)); and was not the recipient of significant payments of other sorts (as defined in 21 CFR 54.2(f)).

☐ (3) As the applicant who is submitting a study or studies sponsored by a firm or party other than the applicant, I certify that I have acted with due diligence to obtain from the listed clinical investigators (attach list of names) or from the sponsor the information required under 54.4 and it was not possible to do so. The reason why this information could not be obtained is attached.

NAME	TITLE
Enrico P. Veltri, MD	V.P. Cardiovascular Department
FIRM / ORGANIZATION: SCHERING-PLOUGH RESEARCH INSTITUTE	
SIGNATURE: Enrico P. Veltri	DATE: 9/11/03

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Food and Drug Administration
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Rockville, MD 20857

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DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54.

Name of clinical investigator

Name of clinical study

The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☒ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Enrico P. Veltri, MD	V. P. Cardiovascular Department
FIRM / ORGANIZATION: Schering-Plough Research Institute	
SIGNATURE: Enrico P Veltri	DATE: 9/11/03

Paperwork Reduction Act Statement

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Food and Drug Administration
5600 Fishers Lane, Room 14-72
Rockville, MD 20857

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Food and Drug Administration

Form Approved: OMB No. 0910-0396
Expiration Date: February 28, 2006

DISCLOSURE: FINANCIAL INTERESTS AND ARRANGEMENTS OF CLINICAL INVESTIGATORS

TO BE COMPLETED BY APPLICANT

The following information concerning _____, who participated as a clinical investigator in the submitted study _____, is submitted in accordance with 21 CFR part 54.

Name of clinical investigator

Name of clinical study

Co-administration Versus Atorvastatin in Hypercholesterolmia PT

54. The named individual has participated in financial arrangements or holds financial interests that are required to be disclosed as follows:

Please mark the applicable checkboxes.

☐ any financial arrangement entered into between the sponsor of the covered study and the clinical investigator involved in the conduct of the covered study, whereby the value of the compensation to the clinical investigator for conducting the study could be influenced by the outcome of the study;

☐ any significant payments of other sorts made on or after February 2, 1999 from the sponsor of the covered study such as a grant to fund ongoing research, compensation in the form of equipment, retainer for ongoing consultation, or honoraria;

☐ any proprietary interest in the product tested in the covered study held by the clinical investigator;

☒ any significant equity interest as defined in 21 CFR 54.2(b), held by the clinical investigator in the sponsor of the covered study.

Details of the individual's disclosable financial arrangements and interests are attached, along with a description of steps taken to minimize the potential bias of clinical study results by any of the disclosed arrangements or interests.

NAME	TITLE
Enrico P. Veltri, MD	V. P. Cardiovascular Department
FIRM / ORGANIZATION: Schering-Plough Research Institute	
SIGNATURE: Enrico Veltri	DATE: 4/11/03

Paperwork Reduction Act Statement

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Number of Pages Redacted 4

❖❖❖

Confidential,
Commercial Information

(H)

THIS SECTION WAS DETERMINED **NOT** TO BE RELEASABLE

3 pages

7-21-04

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
Public Health Service
Food and Drug Administration
Center for Drug Evaluation and Research

DATE: July 21, 2004

FROM: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products

TO: NDA 21-687
Vytorin (Ezetimibe-Simvastatin Tablets)
MSP Singapore
Treatment of hypercholesterolemia

SUBJECT: NDA review issues and recommended action

Background

This product is a fixed-dose combination of Ezetimibe and Simvastatin. These are lipid altering drugs that have additive effects to lower LDL-C and are already approved for use in combination based on the labeling for Zetia (NDA 21-445). The label for Vytorin is supported by information in the NDAs for Zocor and Zetia, to which the sponsor has full right of reference and by additional studies of Vytorin in dyslipidemic patients.

Clinical Efficacy and Safety

The clinical trials database for Vytorin is thoroughly reviewed in Dr. Parks' review. Briefly, based on studies of initial therapy with the combination (either fixed-dose or concomitant dosing), studies of Zetia added to ongoing simvastatin therapy, and long-term studies of the combination, additive effects of the combination relative to either component alone are repeatedly and consistently evident Specifically, adding 10 mg Zetia to doses of simvastatin of 10, 20, 40, and 80 mg daily, results in additional LDL-C lowering from baseline in patients with primary hypercholesterolemia of approximately 15%. As observed in previously reviewed trials of Zetia in combination with other statins (and included in the Zetia label), this additive effect is equivalent to 3 successive doublings of the statin dose. As such, the statin-sparing utility of the combination is an important safety consideration in its use, given the dose-related risks associated with statin therapy, in particular myopathy.

In patients with homozygous familial hypercholesterolemia, the effect of Zetia was also additive to that of simvastatin, lowering LDL-C an average of 23% further from baseline on simvastatin 40 or 80 mg alone.

The sponsor conducted a study comparing Vytorin across the dosage range to atorvastatin 10, 20, 40, and 80 mg daily, demonstrating that Vytorin 20/10 resulting in mean LDL-C lowering from baseline approximately equivalent to that with atorvastatin 80 mg.

Finally, the sponsor studied the lipid altering effects of Vytorin in a population with type 2 diabetes stably treated with simvastatin 20 mg, demonstrating marked further reduction in efficacy of the combination of Vytorin 20/10 compared to next to no effect of increasing the simvastatin dose to 40 mg.

Overall, the safety of combined simvastatin-ezetimibe across all doses is acceptable. The combination does appear associated with some increased incidence of total adverse events in the liver and biliary systems, marked by increased incidence of LFT elevations greater than 3 X ULN. The effect on transaminase elevations appears dose related for the combination as well as for simvastatin monotherapy (this is a statin class effect), with incidence rates of 1-2% for simvastatin 80 mg and up to 5-6% for the combination of Zetia 10 mg and simvastatin 80 mg. No cases of serious liver injury occurred in the clinical trials.

Dr. Parks also notes reports of gallbladder-related AEs in patients treated with Vytorin and ezetimibe. These included cases of cholecystitis leading to cholecystectomy. In animals, ezetimibe causes increased levels of cholesterol in bile, suggested plausibility that this may be a drug effect. This information will be included in the labels for Vytorin and Zetia.

Labeling
The labeling includes relevant information from the labels for Zocor and Zetia as well as that from the studies of combination therapy. Negotiations are complete at this time.

Biopharmaceutics
Vytorin is bioequivalent to co-administered ezetimibe and simvastatin. OCPB recommends approval.

Pharmacology/Toxicology
No novel preclinical findings arise in animals dosed with combination ezetimibe and simvastatin that are not predicted based on the toxicology of the individual drugs. The pharm-tox package is complete and supports the clinical dosing. No further studies are needed. The pharm-tox team recommends approval.

Chemistry/ Microbiology
The application is approvable from the standpoint of ONDC, and the shelf-life granted is 24 months.
The establishment inspections were all acceptable.
A categorical exclusion from the environmental assessment was claimed by the sponsor and granted by the Agency.

DSI/Data Integrity
Two sites were audited involved in the bioequivalence study #039. Forms 483 were issued. The analytical data were deemed acceptable for review.
Financial disclosure
Dr. Parks has reviewed the financial disclosure information and it is acceptable.

ODS/nomenclature
DMETS had no objections to the proposed proprietary name, Vytorin.

Recommendation
Approve.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

David Orloff
7/21/04 07:52:32 PM
MEDICAL OFFICER

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ON ORIGINAL

USER FEE PAYMENT & PDUFA/FDAMA VALIDATION SHEET

Must be completed for ALL original NDAs, efficacy supplements and initial rolling review submissions

NDA # 21-687 SUPP TYPE & # N000 Division 510 UFID # 4597

Applicant Name: MSP Singapore Co., LLC Drug Name: Vytorin (ezetimibe/simvastatin)

For assistance in filling out this form see the Document Processing Manual for complete instructions and examples.

1. **Was a Cover Sheet submitted?**
   [X] Yes [ ] No

2. **Firm in Arrears?**
   [ ] Yes [X] No

3. **Bundling Policy Applied Appropriately? Refer to Draft "Guidance for Industry: Submitting Separate Marketing Applications and Clinical Data for Purposes of Assessing User Fees" http://www.fda.gov/cder/guidance**
   [X] Yes [ ] No (explain in comments)

4. **Administrative Split? (list all NDA#s and Divisions)**

NDA #/Doc Type	Div.	Fee? (Y/N)
N/A		

5. **Type 6?**
   [ ] Yes [X] No

   Type 6 to which other application?

   NDA #_____ Supp Type &#_____

6. **Clinical Data Required for Approval? (Check one)**
   [X] Yes*

   [ ] Yes, by reference to another application

   NDA #_____ Supp Type & #_____

   [ ] No

   * Yes if NDA contains study or literature reports of what are explicitly or implicitly represented by the application to be adequate and well-controlled trials. Clinical data do not include data used to modify the labeling to add a restriction that would improve the safe use of the drug (e.g., adding an adverse reaction, contraindication or warning to the labeling).

7. **505(b)(2) application? (NDA original applications only) Refer to Draft "Guidance for Industry Applications Covered by Section 505(b)(2)" http://www.fda.gov/cder/guidance**
   [ ] Yes [X] No [ ] To be determined

8. **Subpart H (Accelerated Approval/Restricted Distribution)?**
   [ ] Yes [X] No [ ] To be determined

9. **Exclusion from fees? (Circle the appropriate exclusion. For questions, contact User Fee staff)**

   List of exclusions:

   2 – No fee - administrative split
   4 – No fee - 505b2
   7 – Supplement fee - administrative split
   9 – No fee Subpart H supplement– confirmatory study
   11 – No fee Orphan Exception
   13 – No fee State/Federal exemption from fees

10. **Waiver Granted?** N/A
    [ ] Yes (letter enclosed) [ ] No

    Select Waiver Type below: Letter Date: _____

    [ ] Small Business [ ] Barrier-to-Innovation
    [ ] Public Health [ ] Other (explain)

11. **If required, was the appropriate fee paid?**
    [X] Yes [ ] No

12. **Application Review Priority**
    [ ] Priority [X] Standard [ ] To be determined

13. **Fast Track/Rolling Review Presubmission?**
    [ ] Yes [X] No

Comments

/S/ 10/8/03
PM Signature/Date

This form is the initial data extraction of information for both User Fee payment and PDUFA/FDAMA data elements. The information entered may be subject to change due to communication with the User Fee staff. This form will not reflect those changes. Please return this form to your cument room for processing

CC: original archival file
HFD-007

Processor Name & Date

/S/ 9-26-03

QC Name & Date

(8/18/03)

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

Form Approved. OMB No. 0910-0297
Expiration Date: February 29, 2004.

USER FEE COVER SHEET

See Instructions on Reverse Side Before Completing This Form

A completed form must be signed and accompany each new drug or biologic product application and each new supplement. See exceptions on the reverse side. If payment is sent by U.S. mail or courier, please include a copy of this completed form with payment. Payment instructions and fee rates can be found on CDER's website: http://www.fda.gov/cder/pdufa/default.htm

1 APPLICANT'S NAME AND ADDRESS

MSP Singapore Company, LLC
300 Beach Road #12-08
The Concourse
Singapore 199555

U.S. Agent: Diane C. Louie, M.D., M.P.H
Merck & Co., Inc., Rahway, NJ

Attn: Dennis M. Erb, Ph.D.

2. TELEPHONE NUMBER *(Include Area Code)*

(484) 344-7597

3. PRODUCT NAME

VYTORIN™ (ezetimibe/simvastatin combination tablet)

4. BLA SUBMISSION TRACKING NUMBER (STN) / NDA NUMBER

N021687

5. DOES THIS APPLICATION REQUIRE CLINICAL DATA FOR APPROVAL?

☒ YES ☐ NO

IF YOUR RESPONSE IS "NO" AND THIS IS FOR A SUPPLEMENT, STOP HERE AND SIGN THIS FORM.

IF RESPONSE IS 'YES', CHECK THE APPROPRIATE RESPONSE BELOW:

☒ THE REQUIRED CLINICAL DATA ARE CONTAINED IN THE APPLICATION.

☒ THE REQUIRED CLINICAL DATA ARE SUBMITTED BY REFERENCE TO:

N021445, N019766
(APPLICATION NO. CONTAINING THE DATA).

6 USER FEE I D NUMBER

4597

7 IS THIS APPLICATION COVERED BY ANY OF THE FOLLOWING USER FEE EXCLUSIONS? IF SO, CHECK THE APPLICABLE EXCLUSION.

☐ A LARGE VOLUME PARENTERAL DRUG PRODUCT APPROVED UNDER SECTION 505 OF THE FEDERAL FOOD, DRUG, AND COSMETIC ACT BEFORE 9/1/92 *(Self Explanatory)*

☐ A 505(b)(2) APPLICATION THAT DOES NOT REQUIRE A FEE *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION QUALIFIES FOR THE ORPHAN EXCEPTION UNDER SECTION 736(a)(1)(E) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS A PEDIATRIC SUPPLEMENT THAT QUALIFIES FOR THE EXCEPTION UNDER SECTION 736(a)(1)(F) of the Federal Food, Drug, and Cosmetic Act *(See item 7, reverse side before checking box.)*

☐ THE APPLICATION IS SUBMITTED BY A STATE OR FEDERAL GOVERNMENT ENTITY FOR A DRUG THAT IS NOT DISTRIBUTED COMMERCIALLY *(Self Explanatory)*

8. HAS A WAIVER OF AN APPLICATION FEE BEEN GRANTED FOR THIS APPLICATION?

☐ YES ☒ NO

(See item 8, reverse side if answered YES)

SIGNATURE OF AUTHORIZED COMPANY REPRESENTATIVE	TITLE	DATE
Dennis M. Erb	Dennis M. Erb, Ph.D. Executive Director, Regulatory Affairs	9/5/03

NDA/EFFICACY SUPPLEMENT ACTION PACKAGE CHECKLIST

Application Information		
NDA 21-687	Efficacy Supplement Type SE-	Supplement Number
Drug: Vytorin (ezetimibe/simvastatin) 10/10, 10/20, 10/40, 10/80 mg tablets		Applicant: MSP Singapore, LLC, a joint venture b/w Merck & Co. and Schering Corporation
RPM: Monika Johnson	HFD-510	Phone # 301-827-9087
Application Type: (X) 505(b)(1) ( ) 505(b)(2) (This can be determined by consulting page 1 of the NDA Regulatory Filing Review for this application or Appendix A to this Action Package Checklist.) **If this is a 505(b)(2) application, please review and confirm the information previously provided in Appendix B to the NDA Regulatory Filing Review. Please update any information (including patent certification information) that is no longer correct.** ( ) Confirmed and/or corrected	Listed drug(s) referred to in 505(b)(2) application (NDA #(s), Drug name(s)):	

❖ Application Classifications:	
• Review priority	(X) Standard ( ) Priority
• Chem class (NDAs only)	4S
• Other (e.g., orphan, OTC)	n/a
❖ User Fee Goal Dates	July 24, 2004
❖ Special programs (indicate all that apply)	(X) None Subpart H ( ) 21 CFR 314.510 (accelerated approval) ( ) 21 CFR 314.520 (restricted distribution) ( ) Fast Track ( ) Rolling Review ( ) CMA Pilot 1 ( ) CMA Pilot 2
❖ User Fee Information	
• User Fee	(X) Paid UF ID number 4697
• User Fee waiver	( ) Small business ( ) Public health ( ) Barrier-to-Innovation ( ) Other (specify)
• User Fee exception	( ) Orphan designation ( ) No-fee 505(b)(2) (see NDA Regulatory Filing Review for instructions) ( ) Other (specify)
• Application Integrity Policy (AIP)	
• Applicant is on the AIP	( ) Yes (X) No

• This application is on the AIP	( ) Yes (X) No
• Exception for review (Center Director's memo)	
• OC clearance for approval	n/a
❖ Debarment certification: verified that qualifying language (e.g., willingly, knowingly) was not used in certification & certifications from foreign applicants are cosigned by US agent.	(X) Verified
❖ Patent	
• Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought.	(X) Verified
• Patent certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent.	21 CFR 314.50(i)(1)(*i*)(A) ( ) Verified 21 CFR 314.50(i)(1) ( ) (ii) ( ) (iii)
• [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval).	
• [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). *(If the application does not include any paragraph IV certifications, mark "N/A" and skip to the next box below (Exclusivity)).*	( ) N/A (no paragraph IV certification) ( ) Verified
• [505(b)(2) applications] For each paragraph IV certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation. Answer the following questions for each paragraph IV certification:	
(1) Have 45 days passed since the patent owner's receipt of the applicant's notice of certification? (Note: The date that the patent owner received the applicant's notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e))). *If "**Yes**," skip to question (4) below. If "**No**," continue with question (2).*	( ) Yes ( ) No
(2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant's notice of certification, as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**No**," continue with question (3).*	( ) Yes ( ) No
(3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?	( ) Yes ( ) No

(Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2))). *If "No," the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.* (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)? *If "**Yes**," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "No," continue with question (5).* (5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification? (Note: This can be determined by confirming whether the Division has received a written notice from the applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period). *If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next box below (Exclusivity).* *If "**Yes**," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007) and attach a summary of the response.*	( ) Yes ( ) No ( ) Yes ( ) No
❖ Exclusivity (approvals only)	
• Exclusivity summary • Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? (Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)	n/a
• Is there existing orphan drug exclusivity protection for the "same drug" for the proposed indication(s)? *Refer to 21 CFR 316.3(b)(13) for the definition of "same drug" for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.*	( ) Yes, Application #_____ ( ) No
❖ Administrative Reviews (Project Manager, ADRA) *(indicate date of each review)*	

General Information	
❖ Actions	
• Proposed action	(X) AP ( ) TA ( ) AE ( ) NA
• Previous actions (specify type and date for each action taken)	
• Status of advertising (approvals only)	( ) Materials requested in AP letter ( ) Reviewed for Subpart H
❖ Public communications	
• Press Office notified of action (approval only)	(X) Yes ( ) Not applicable
• Indicate what types (if any) of information dissemination are anticipated	( ) None (X) Press Release ( ) Talk Paper ( ) Dear Health Care Professional Letter
❖ Labeling (package insert, patient package insert (if applicable), MedGuide (if applicable))	
• Division's proposed labeling (only if generated after latest applicant submission of labeling)	
• Most recent applicant-proposed labeling	
• Original applicant-proposed labeling	September 23, 2003
• Labeling reviews (including DDMAC, DMETS, DSRCS) and minutes of labeling meetings *(indicate dates of reviews and meetings)*	DDMAC, DSRCS
• Other relevant labeling (e.g., most recent 3 in class, class labeling)	
❖ Labels (immediate container & carton labels)	
• Division proposed (only if generated after latest applicant submission)	
• Applicant proposed	September 23, 2003
• Reviews	DSRCS, CMC, CSO
❖ Post-marketing commitments	
• Agency request for post-marketing commitments	n/a
• Documentation of discussions and/or agreements relating to post-marketing commitments	
❖ Outgoing correspondence (i.e., letters, E-mails, faxes)	
❖ Memoranda and Telecons	
❖ Minutes of Meetings	
• EOP2 meeting (indicate date)	December 16, 2002
• Pre-NDA meeting (indicate date)	
• Pre-Approval Safety Conference (indicate date; approvals only)	
• Other (Guidance)	November 14, 2002
❖ Advisory Committee Meeting	
• Date of Meeting	n/a
• 48-hour alert	
❖ Federal Register Notices, DESI documents, NAS/NRC reports (if applicable)	n/a

Summary Application Review	
❖ Summary Reviews (e.g., Office Director, Division Director, Medical Team Leader) *(indicate date for each review)*	
Clinical Information	
❖ Clinical review(s) *(indicate date for each review)*	7/16/04
❖ Microbiology (efficacy) review(s) *(indicate date for each review)*	n/a
❖ Safety Update review(s) *(indicate date or location if incorporated in another review)*	See MAR 7/16/04
❖ Risk Management Plan review(s) *(indicate date/location if incorporated in another rev)*	n/a
❖ Pediatric Page(separate page for each indication addressing status of all age groups)	
❖ Demographic Worksheet *(NME approvals only)*	n/a
❖ Statistical review(s) *(indicate date for each review)*	July 15, 2004
❖ Biopharmaceutical review(s) *(indicate date for each review)*	June 21, 2004
❖ Controlled Substance Staff review(s) and recommendation for scheduling *(indicate date for each review)*	n/a
❖ Clinical Inspection Review Summary (DSI)	
• Clinical studies	
• Bioequivalence studies	
CMC Information	
❖ CMC review(s) *(indicate date for each review)*	
❖ Environmental Assessment	
• Categorical Exclusion *(indicate review date)*	
• Review & FONSI *(indicate date of review)*	n/a
• Review & Environmental Impact Statement *(indicate date of each review)*	n/a
❖ Microbiology (validation of sterilization & product sterility) review(s) *(indicate date for each review)*	n/a
❖ Facilities inspection (provide EER report)	Date completed: ( ) Acceptable ( ) Withhold recommendation
❖ Methods validation	( ) Completed ( ) Requested ( ) Not yet requested
Nonclinical Pharm/Tox Information	
❖ Pharm/tox review(s), including referenced IND reviews *(indicate date for each review)*	March 30, 2004
❖ Nonclinical inspection review summary	n/a
❖ Statistical review(s) of carcinogenicity studies *(indicate date for each review)*	n/a
❖ CAC/ECAC report	n/a

CMC not ready at review

EES- emails; goal date July 16, 2004 inspection date, to be have the tentative results; in writing (Refuse email)

Appendix A to NDA/Efficacy Supplement Action Package Checklist

An application is likely to be a 505(b)(2) application if:

(1) it relies on literature to meet any of the approval requirements (unless the applicant has a written right of reference to the underlying data)
(2) it relies on the Agency's previous approval of another sponsor's drug product (which may be evidenced by reference to publicly available FDA reviews, or labeling of another drug sponsor's drug product) to meet any of the approval requirements (unless the application includes a written right of reference to data in the other sponsor's NDA)
(3) it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)
(4) it seeks approval for a change from a product described in an OTC monograph and relies on the monograph to establish the safety or effectiveness of one or more aspects of the drug product for which approval is sought (see 21 CFR 330.11).

Products that may be likely to be described in a 505(b)(2) application include combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations), OTC monograph deviations, new dosage forms, new indications, and new salts.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, please consult with the Director, Division of Regulatory Policy II, Office of Regulatory Policy (HFD-007).

NDA REGULATORY FILING REVIEW
(Including Memo of Filing Meeting)

NDA # 21-687

Trade Name: Vytorin (ezetimibe/simvastatin) Tablets
Generic Name: ezetimibe/simvastatin
Strengths: ezetimibe 10 mg/ simva 10 mg, ezetimibe 10 mg/simva 20 mg, ezetimibe 10 mg/simva40 mg, ezetimibe 10 mg/simva 80 mg

Applicant: MSP Singapor, LLC.

Date of Application: September 24, 2003
Date of Receipt: September 24, 2003
Date clock started after UN: N/A
Date of Filing Meeting: October 28, 2003
Filing Date: November 23, 2003
Action Goal Date (optional): User Fee Goal Date: July 24, 2004

Indication(s) requested: indicated as adjunctive therapy to diet for the reduction of elevated total-C, LDL-C, Apo-B, TG, and non-HDL-C, and to increase HDL-C in patients with primary (heterozygous familial and non-familial) hypercholesterolemia or mixed hyperlipidemia.

Type of Original NDA: (b)(1) X (b)(2) _____
OR
Type of Supplement: (b)(1) _____ (b)(2) _____
NOTE: A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). If the application is a (b)(2) application, complete the (b)(2) section at the end of this review.

Therapeutic Classification: S X P _____
Resubmission after withdrawal? N/A Resubmission after refuse to file? N/A
Chemical Classification: (1,2,3 etc) 3
Other (orphan, OTC, etc.) N/A

User Fee Status: Paid 9/10/03 ✓ Exempt (orphan, government) N/A
Waived (e g., small business, public health) N/A

Form 3397 (User Fee Cover Sheet) submitted: YES
User Fee ID # 4697
Clinical data? YES _____ NO, Referenced to NDA # _____

Is there any 5-year or 3-year exclusivity on this active moiety in either a (b)(1) or a (b)(2) application? NO

If yes, explain:

Does another drug have orphan drug exclusivity for the same indication? NO

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If yes, is the drug considered to be the same drug according to the orphan drug definition of sameness [21 CFR 316.3(b)(13)]?

N/A

Is the application affected by the Application Integrity Policy (AIP)? NO
If yes, explain.

If yes, ~~has OC/DMPQ been notified of the submission?~~ YES ~~NO~~

- Does the submission contain an accurate comprehensive index? YES
- Was form 356h included with an authorized signature? YES
  If foreign applicant, both the applicant and the U.S. agent must sign.
- Submission complete as required under 21 CFR 314.50? YES
  If no, explain:
- If an electronic NDA, does it follow the Guidance? YES ELECTRONIC
  If an electronic NDA, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?
  Clinstat, Chemistry, Financial Disclosure, Labeling, PharmTox, Case Report Tables, Case Report Forms, HP/Bio, Summary, Administrative Documents
  Additional comments:
  Follows eNDA guidance and is formatted according to CTD.
- If in Common Technical Document format, does it follow the guidance? YES
- Is it an electronic CTD? NO
  If an electronic CTD, all certifications must be in paper and require a signature.
  Which parts of the application were submitted in electronic format?

  Additional comments.

- Patent information submitted on form FDA 3542a? YES
- Exclusivity requested? NO
  Note: An applicant can receive exclusivity without requesting it; therefore, requesting exclusivity is not required.

- Correctly worded Debarment Certification included with authorized signature? YES
  If foreign applicant, both the applicant and the U.S. Agent must sign the certification.

  NOTE: Debarment Certification should use wording in FD&C Act section 306(k)(1) i e.,

"[Name of applicant] hereby certifies that it did not and will not use in any capacity the services of any person debarred under section 306 of the Federal Food, Drug, and Cosmetic Act in connection with this application." Applicant may not use wording such as "To the best of my knowledge . . . ."

- Financial Disclosure forms included with authorized signature? YES
  (Forms 3454 and 3455 must be used and must be signed by the APPLICANT.)
- Field Copy Certification (that it is a true copy of the CMC technical section)? YES

Refer to 21 CFR 314.101(d) for Filing Requirements

- PDUFA and Action Goal dates correct in COMIS? YES
  If not, have the document room staff correct them immediately. These are the dates EES uses for calculating inspection dates.
- Drug name/Applicant name correct in COMIS? If not, have the Document Room make the corrections. YES
- List referenced IND numbers: IND 65,066
- End-of-Phase 2 Meeting(s)? Date(s) 12/16/02
  If yes, distribute minutes before filing meeting.
- Pre-NDA Meeting(s)? Date(s) _____ NO
  If yes, distribute minutes before filing meeting.

Project Management

- All labeling (PI, PPI, MedGuide, carton and immediate container labels) consulted to DDMAC? YES
- Trade name (plus PI and all labels and labeling) consulted to ODS/DMETS? YES
- MedGuide and/or PPI (plus PI) consulted to ODS/DSRCS? N/A
- If a drug with abuse potential, was an Abuse Liability Assessment, including a proposal for scheduling, submitted? N/A

If Rx-to-OTC Switch application:

- OTC label comprehension studies, all OTC labeling, and current approved PI consulted to ODS/DSRCS? N/A
- Has DOTCDP been notified of the OTC switch application? N/A

Clinical

- If a controlled substance, has a consult been sent to the Controlled Substance Staff? N/A

Chemistry

- Did applicant request categorical exclusion for environmental assessment? YES
  If no, did applicant submit a complete environmental assessment? N/A
  If EA submitted, consulted to Nancy Sager (HFD-357)? YES NO
- Establishment Evaluation Request (EER) submitted to DMPQ? (YES) NO
- If a parenteral product, consulted to Microbiology Team (HFD-805)? N/A

If 505(b)(2) application, complete the following section: N/A

- Name of listed drug(s) and NDA/ANDA #:
- Describe the change from the listed drug(s) provided for in this (b)(2) application (for example, "This application provides for a new indication, otitis media" or "This application provides for a change in dosage form, from capsules to solution").
- Is the application for a duplicate of a listed drug and eligible for approval under section 505(j) as an ANDA? (Normally, FDA will refuse-to-file such NDAs.)

  N/A
- Is the extent to which the active ingredient(s) is absorbed or otherwise made available to the site of action less than that of the reference listed drug (RLD)? (See 314.54(b)(1)). If yes, the application should be refused for filing under 314.101(d)(9).

  N/A
- Is the rate at which the product's active ingredient(s) is absorbed or otherwise made available to the site of action unintentionally less than that of the RLD? (See 314.54(b)(2)). If yes, the application should be refused for filing under 314.101(d)(9).

  N/A
- Which of the following patent certifications does the application contain? Note that a patent certification must contain an authorized signature.

  ____ 21 CFR 314.50(i)(1)(i)(A)(1): The patent information has not been submitted to FDA.

  ____ 21 CFR 314 50(i)(1)(i)(A)(2): The patent has expired.

  ____ 21 CFR 314.50(i)(1)(i)(A)(3): The date on which the patent will expire.

  ____ 21 CFR 314.50(i)(1)(i)(A)(4): The patent is invalid, unenforceable, or will not be infringed by the manufacture, use, or sale of the drug product for which the application is submitted.

  IF FILED, and if the applicant made a "Paragraph IV" certification [21 CFR 314.50(i)(1)(i)(A)(4)], the applicant must submit a signed certification that the patent holder was notified the NDA was filed [21 CFR 314 52(b)]. Subsequently, the applicant must submit documentation that the patent holder(s) received the notification ([21 CFR 314 52(e)]

  ____ 21 CFR 314.50(i)(1)(ii): No relevant patents.

____ 21 CFR 314.50(i)(1)(iii): The patent on the listed drug is a method of use patent and the labeling for the drug product for which the applicant is seeking approval does not include any indications that are covered by the use patent. Applicant must provide a statement that the method of use patent does not claim any of the proposed indications.

Formatted: Bullets and Numbering

____ 21 CFR 314.50(i)(3): Statement that applicant has a licensing agreement with the patent owner (must also submit certification under 21 CFR 314.50(i)(1)(i)(A)(4) above.)

____ Written statement from patent owner that it consents to an immediate effective date upon approval of the application.

- Did the applicant:
  - Identify which parts of the application rely on information the applicant does not own or to which the applicant does not have a right of reference?

    N/A
  - Submit a statement as to whether the listed drug(s) identified has received a period of marketing exclusivity?

    N/A
  - Submit a bioavailability/bioequivalence (BA/BE) study comparing the proposed product to the listed drug?

    N/A
  - Certify that it is seeking approval only for a new indication and not for the indications approved for the listed drug if the listed drug has patent protection for the approved indications and the applicant is requesting only the new indication (21 CFR 314.54(a)(1)(iv) ?

    N/A
- If the (b)(2) applicant is requesting exclusivity, did the applicant submit the following information required by 21 CFR 314.50(j)(4).
  - Certification that each of the investigations included meets the definition of "new clinical investigation" as set forth at 314.108(a).

    N/A
  - A list of all published studies or publicly available reports that are relevant to the conditions for which the applicant is seeking approval.

    N/A
  - EITHER
    The number of the applicant's IND under which the studies essential to approval were conducted.

    N/A

    OR

    A certification that it provided substantial support of the clinical investigation(s) essential to approval if it was not the sponsor of the IND under which those clinical studies were conducted?

    N/A
- Has the Director, Div. of Regulatory Policy II, HFD-007, been notified of the existence of the (b)(2) application?

  N/A

ATTACHMENT

MEMO OF FILING MEETING

DATE: October 28, 2003

BACKGROUND:
NDA 21-687/Vytorin, is indicated for the treatment of hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH). The combination product strengths are ezetimibe 10mg and simvastatin 10mg, 20mg, 40mg, and 80mg Tablets. Reference is made to the Investigational New Drug (IND) 52, 791 and New Drug Application (NDA) 21-445 Zetia (ezetimibe), and to IND 25, 742 and NDA 19-766 Zocor (simvastatin).

ATTENDEES: Mary Parks, M D
Wei Qiu, Ph.D.
Sharon Kelly, Ph.D.
Karen Davis Bruno, Ph.D.
Kati Johnson
Hae Young Ahn, Ph.D.
Stephen Moore, Ph.D.
Indra Antonipillai, Ph.D
Valerie Jimenez

ASSIGNED REVIEWERS:

Discipline	Reviewer
Medical:	Mary Parks, M.D
Pharmacology:	Indra Antonipillai, Ph.D/Karen Davis Bruno, Ph.D.
Chemistry:	Sharon Kelly, Ph.D./Stephen Moore, Ph.D.
Environmental Assessment (if needed):	
Biopharmaceutical:	Wei Qiu, Ph.D./Hae Young Ahn, Ph.D.
DSI:	
Regulatory Project Management:	Valerie Jimenez/Kati Johnson

Per reviewers, are all parts in English or English translation? YES
If no, explain:

CLINICAL FILE __X__ REFUSE TO FILE _____

- Clinical site inspection needed: NO
- Advisory Committee Meeting needed? NO
- If the application is affected by the AIP, has the division made a recommendation regarding whether or not an exception to the AIP should be granted to permit review based on medical necessity or public health significance?

  N/A

CLINICAL MICROBIOLOGY NA __X__ FILE _____ REFUSE TO FILE _____

STATISTICS N/A __X__ FILE _____ REFUSE TO FILE _____

BIOPHARMACEUTICS FILE __X__ REFUSE TO FILE _____

Version: 9/25/03

APPEARS THIS WAY
ON ORIGINAL

- Biopharm. inspection needed: YES

PHARMACOLOGY N/A _____ FILE __X____ REFUSE TO FILE _____

- GLP inspection needed: NO

CHEMISTRY FILE __X___ REFUSE TO FILE _____

- Establishment(s) ready for inspection? YES
- Microbiology NO

ELECTRONIC SUBMISSION:
Any comments:

REGULATORY CONCLUSIONS/DEFICIENCIES:

_____ The application is unsuitable for filing. Explain why.

__X___ The application, on its face, appears to be well organized and indexed. The application appears to be suitable for filing.

__X____ No filing issues have been identified.

_____ Filing issues to be communicated by Day 74. List (optional):

ACTION ITEMS:

1. If RTF, notify everybody who already received a consult request of the RTF action. Cancel the EER.
2. If filed and the application is under the AIP, prepare a letter either granting (for signature by Center Director) or denying (for signature by ODE Director) an exception for review.
3. Document filing issues/no filing issues conveyed to applicant by Day 74.

_____
Valerie Jimenez
Regulatory Project Manager, HFD-510

in response to Filing letter 11/26

DEPARTMENT OF HEALTH AND HUMAN SERVICES
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG, BIOLOGIC, OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, Parts 314 & 601)

Form Approved: OMB No. 0910-0338
Expiration Date: August 31, 2006
See OMB Statement on page 2.

FOR FDA USE ONLY

APPLICATION NUMBER

APPLICANT INFORMATION

NAME OF APPLICANT	DATE OF SUBMISSION
MSP Singapore Company, LLC	September 24, 2003
TELEPHONE NO. *(include Area Code)* 732-594-7186	FACSIMILE (FAX) *Number (include Area Code)* 732-594-1030
APPLICANT ADDRESS *(Number, Street, City, State, Country, ZIP Code or Mail Code, and U.S. License number if previously issued):* 300 Beach Road #12-08 The Concourse Singapore 199555	AUTHORIZED U.S. AGENT NAME & ADDRESS *(Number, Street, City, State, ZIP Code, telephone & FAX number)* IF APPLICABLE Diane Louie, M.D., M.P.H. Associate Director, Regulatory Affairs Agent for the MSP Singapore Company, LLC

PRODUCT DESCRIPTION

NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER, OR BIOLOGICS LICENSE APPLICATION NUMBER *(If previously issued)* 21-687

ESTABLISHED NAME *(e.g., Proper name, USP/USAN name)*	PROPRIETARY NAME *(trade name)* IF ANY
ezetimibe/simvastatin combination tablet	VYTORIN™

CHEMICAL/BIOCHEMICAL/BLOOD PRODUCT NAME *(if any)* ezetimibe: 1-(4-Fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone
simvastatin: [1S-[1α, 3α, 7β, 8β(2S*, 4S*), 8αβ]]-1,2,3,7,8a-hexahydro-3,7-dimethyl-8-[2-tetrahydro-4-hydroxy-6-ozo-2H-pyran-2-yl)ethyl]-1-napthalenyl-2,2-dimethylbutanoate

CODE NAME *(If any)* MK-0653A

DOSAGE FORM	STRENGTHS:	ROUTE OF ADMINISTRATION.
Tablet	ezetimibe 10 mg and simvastatin 10mg, 20 mg, 40 mg or 80 mg	Oral

(PROPOSED) INDICATION(S) FOR USE:
Primary Hypercholesterolemia and Homozygous Familial Hypercholesterolemia (HoFH)

APPLICATION INFORMATION

APPLICATION TYPE
(check one) ☒ NEW DRUG APPLICATION (21 CFR 314.50) ☐ ABBREVIATED NEW DRUG APPLICATION (ANDA, 21 CFR 314.94)
☐ BIOLOGICS LICENSE APPLICATION (21 CFR Part 601)

IF AN NDA, IDENTIFY THE APPROPRIATE TYPE ☒ 505 (b)(1) ☐ 505 (b)(2)

IF AN ANDA, OR 505(b)(2), IDENTIFY THE REFERENCE LISTED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION
Name of Drug Holder of Approved Application

TYPE OF SUBMISSION (check one) ☒ ORIGINAL APPLICATION ☐ AMENDMENT TO A PENDING APPLICATION ☐ RESUBMISSION
☐ PRESUBMISSION ☐ ANNUAL REPORT ☐ ESTABLISHMENT DESCRIPTION SUPPLEMENT ☐ EFFICACY SUPPLEMENT
☐ LABELING SUPPLEMENT ☐ CHEMISTRY MANUFACTURING AND CONTROLS SUPPLEMENT ☐ OTHER

IF A SUBMISSION OF PARTIAL APPLICATION, PROVIDE LETTER DATE OF AGREEMENT TO PARTIAL SUBMISSION:

IF A SUPPLEMENT, IDENTIFY THE APPROPRIATE CATEGORY ☐ CBE ☐ CBE-30 ☐ Prior Approval (PA)

REASON FOR SUBMISSION

PROPOSED MARKETING STATUS *(check one)* ☒ PRESCRIPTION PRODUCT *(Rx)* ☐ OVER THE COUNTER PRODUCT (OTC)

NUMBER OF VOLUMES SUBMITTED 1 THIS APPLICATION IS ☐ PAPER ☒ PAPER AND ELECTRONIC ☐ ELECTRONIC

ESTABLISHMENT INFORMATION (Full establishment information should be provided in the body of the Application.)
Provide locations of all manufacturing, packaging and control sites for drug substance and drug product (continuation sheets may be used if necessary). Include name, address, contact, telephone number, registration number (CFN), DMF number, and manufacturing steps and/or type of testing (e.g. Final dosage form, Stability testing) conducted at the site. Please indicate whether the site is ready for inspection or, if not, when it will be ready.

The 356h Attachment provides the establishment and PAI readiness information for this product.

Cross References (list related License Applications, INDs, NDAs, PMAs, 510(k)s, IDEs, BMFs, and DMFs referenced in the current application)

IND 65,066 (MK-0653A, ezetimibe/simvastatin combination tablet); IND 52,791 (ezetimibe); NDA 21-445 ZETIA™; IND 25,742 (MK-0733, simvastatin); NDA 19-766 ZOCOR™
DMFs referenced in this application are listed on the Attachment to this 356h form.

This application contains the following items: *(Check all that apply)*	
X	1. Index
X	2. Labeling *(check one)* ☒ Draft Labeling ☐ Final Printed Labeling
X	3. Summary (21 CFR 314.50 (c))
X	4. Chemistry section
X	A. Chemistry, manufacturing, and controls information (e.g., 21 CFR 314.50(d)(1); 21 CFR 601.2)
	B. Samples (21 CIFIR 314.50 (e)(1); 21 CFR 601.2 (a)) (Submit only upon FDA's request)
X	C. Methods validation package (e.g., 21 CFR 314.50(e)(2)(i); 21 CFR 601.2)
X	5. Nonclinical pharmacology and toxicology section (e.g., 21 CFR 314.50(d)(2); 21 CFR 601.2)
X	6. Human pharmacokinetics and bioavailability section (e.g., 21 CFR 314.50(d)(3); 21 CFR 601.2)
	7. Clinical Microbiology (e.g., 21 CFR 314.50(d)(4))
X	8. Clinical data section (e.g., 21 CFR 314.50(d)(5); 21 CFR 601.2)
	9. Safety update report (e.g., 21 CFR 314.50(d)(5)(vi)(b); 21 CFR 601.2)
X	10. Statistical section (e.g., 21 CFR 314.50(d)(6); 21 CFR 601.2)
X	11. Case report tabulations (e.g., 21 CFR 314.50(f)(1); 21 CFR 601.2)
X	12. Case report forms (e.g., 21 CFR 314.50 (f)(2); 21 CFR 601-2)
X	13. Patent information on any patent which claims the drug (21 U.S.C. 355(b) or (c))
	14. A patent certification with respect to any patent which claims the drug (21 U.S.C. 355 (b)(2) or 0)(2)(A))
	15. Establishment description (21 CFR Part 600, if applicable)
X	16. Debarment certification (FD&C Act 306 (k)(1))
X	17. Field copy certification (21 CFR 314.50 (k)(3))
X	18. User Fee Cover Sheet (Form FDA 3397)
X	19. Financial Information (21 CFR Part 54)
X	20. OTHER (Specify) Pediatric Waiver, Regulatory Background Information, Letters of Authorization

CERTIFICATION

I agree to update this application with new safety information about the product that may reasonably affect the statement of contra i nd ications, warnings, precautions, or adverse reactions in the draft labeling. I agree to submit safety update reports as provided for by regulation or as requested by FDA. If this application is approved, I agree to comply with all applicable laws and regulations that apply to approved applications, including, but not limited to the following:

1. Good manufacturing practice regulations in 21 CFR Parts 210, 211 or applicable regulations, Parts 606, and/or 820.
2. Biological establishment standards in 21 CFR Part 600.
3. Labeling regulations in 21 CFR Parts 201, 606, 610, 660, and/or 809.
4. In the case of a prescription drug or biological product, prescription drug advertising regulations in 21 CFR Part 202.
5. Regulations on making changes in application in FD&C Act Section 506A, 21 CFR 314.71, 314.72, 314.97, 314.99, and 601.12.
6. Regulations on Reports in 21 CFR 314.80, 314.81, 600.80, and 600.81.
7. Local, state and Federal environmental impact laws.

If this application applies to a drug product that FDA has proposed for scheduling under the Controlled Substances Act, I agree not to market the product until the Drug Enforcement Administration makes a final scheduling decision.

The data and information in this submission have been reviewed and, to the best of my knowledge are certified to be true and accurate.

Warning: A willfully false statement is a criminal offense, U.S. Code, title 18, section 1001.

SIGNATURE OF RESPONSIBLE OFFICIAL OR AGENT	TYPED NAME AND TITLE	DATE
Rene Cloutier, MD, MPH	Mr. Robert A. McMahon Vice President & General Manager MSP Singapore Company, LLC Diane Louie, M.D., M.P.H. Associate Director, Regulatory Affairs Agent for the MSP Singapore Company, LLC	Sept. 24, 2003

ADDRESS *(Street, City, State, and ZIP Code)*	Telephone Number
Merck & Co., Inc. P.O. Box 2000, RY 33-200 Rahway, NJ 07065	(732) 594-7186

Public reporting burden for this collection of information is estimated to average 24 hours per response, including the time for reviewing instructions, searching existing data sources, gathering and maintaining the data needed, and completing and reviewing the collection of information. Send comments regarding this burden estimate or any other aspect of this collection of information, including suggestions for reducing this burden to:

Department of Health and Human Services
Food and Drug Administration
CDER, HFD-99
1401 Rockville Pike
Rockville, MD 20852-1448

Food and Drug Administration
CDER (HFD-94)
12229 Wilkins Avenue
Rockville, MD 20852

An agency may not conduct or sponsor, and a person is not required to respond to, a collection of information unless it displays a currently valid OMB control number.

11/26/03

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service
Food and Drug Administration
Rockville, MD 20857

FILING REVIEW LETTER

NDA 21-687

Merck & Co., Inc. Agent for
MSP Singapore Co., LLC
Attention: Diane C. Louie, M.D., M.P.H.
Associate Director, Regulatory Affairs
P. O. Box 2000, RY 33-200
Rahway, NJ 07065

Dear Dr. Louie:

Please refer to your September 24, 2003, new drug application (NDA) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Vytorin (ezetimibe/simvastatin) Tablets, 10/10 mg, 10/20 mg, 10/40 mg, and 10/80 mg.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, this application was filed under section 505(b) of the Act on November 23, 2003, in accordance with 21 CFR 314.101(a). However, we have the following comments and requests:

1. The dissolution study was conducted in [redacted] using USP apparatus II (paddle) at 50 rpm. To optimize the dissolution method for quality control purposes, as well as for granting biowaiver to strengths ezetimibe 10mg/simvastatin 20mg and ezetimibe 10mg/simvastatin 40mg, we recommend you investigate two other conditions, such as a lower SLS level. You must submit the dissolution profiles for all strength tablets from 3 batches under three different conditions.
2. Please submit a Debarment Certification and 356h form signed by both the applicant and agent.

submit 12/4/03

At this time, we have not identified any potential filing review issues. Our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

If you have any questions, call Valerie Jimenez, Regulatory Project Manager, at (301) 827-9090.

Sincerely,

{See appended electronic signature page}

Enid Galliers
Chief, Project Management Staff
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/
Valerie Jimenez
11/26/03 11:25:16 AM
Signing for Enid Galliers, Chief, Project Management Staff

APPEARS THIS WAY
ON ORIGINAL

10/30/03

NDA 21-687/Filing

Review completed 10/27/03
Signed off in DFS on

45 Day Meeting Checklist
NONCLINICAL PHARMACOLOGY/TOXICOLOGY

NDA 21-687: This NDA is a 505(b)(1) application.
Submission date: 9/24/2003
Sponsor: MSP Singapore Company, LLC, Singapore.
Drug: Vytorin (ezetimibe/simvastatin combination tablet, with code name MK-0653A).
Introduction: This tablet is a combination of two approved drug products, ezetimibe (a selective inhibitor of intestinal cholesterol/phytosterol) and simvastatin (an HMG-CoA reductase inhibitor). Ezetimibe (NDA 21-445) and simvastatin (NDA 19-766) are both marketed drugs. The combination product in the current NDA is proposed for patients with primary hypercholesterolemia (including homozygous, and heterozygous familial hypercholesterolemia and mixed hyperlipidemia).

The excipients that are used in the combination tablet formulation have been used in either the ezetimibe tablet or simvastatin tablet formulation, with the exception of [redacted] propyl gallate and [redacted] hydroxypropyl methylcellulose.

ITEM: NDA 21-687	**YES**	**NO**	**COMMENT**
1) Does this section of the NDA appear to be organized (according to 21 CFR 314 and current guidelines for format and content) in a manner that would allow a substantive review to be completed?	Yes		
2) Is this section of the NDA indexed and paginated in a manner to enable a timely and substantive review?	Yes		
3) Is this section of the NDA sufficiently legible so that a substantive review can be done? Has the data been presented in an appropriate manner (consider tables, graphs, complete study reports, inclusion of individual animal data, appropriate data analysis, etc.)?	Yes		The sponsor had previously provided 3-month rat as well as 3 & 6-month dog toxicity studies with ezetimibe + simvastatin combination in animals in NDA 21-445. In the current NDA submission, sponsor has provided a 14-month toxicity/toxicokinetics study of the above two drugs in dogs. All other studies with the combination have already been conducted under NDA 21-445, in which ezetimibe was approved for monotherapy and combination therapy with statins (simvastatin, atorvastatin, pravastatin and lovastatin).

4) Are all necessary and appropriate studies for this agent, including special studies/data requested by the Division during pre-submission communications/discussions, completed and submitted in this NDA? Please itemize the critical studies included and indicate any significant studies that were omitted from the NDA (genotox, reprotox, adequate duration of chronic tox, carcinogenicity)	Yes		Have electronic files of the carcinogenicity studies been submitted for statistical review? No carcinogenicity or other preclinical studies were requested with the current combination formulation, as both drugs are approved drug products. However, sponsor has conducted one 14-month toxicity study in dogs. All the non-clinical studies have already been conducted with the approved ezetimibe (NDA 21-445) and approved simvastatin (NDA 19-766), and are not considered necessary for the combination tablets (ezetimibe /simvastatin).

ITEM	YES	NO	COMMENT
5) Were the studies adequately designed (i.e., appropriate number of animals, adequate monitoring consistent with the proposed clinical use, state-of-the art protocols, etc.)?			Yes. As indicated earlier, all non-clinical studies with ezetimibe + simvastatin have been conducted under the approved NDA 21-445, and these were adequately designed.
6) If the formulation to be marketed is not identical to the formulation used in the toxicology studies (including the impurity profiles), has the sponsor clearly defined the differences and submitted reviewable supportive data (i.e., adequate repeat studies using the marketed product and/or adequate justification for why such repetition would not be necessary)?	Yes		Sponsor has used basically the same formulation in the current product, as used previously for ezetimibe and simvastatin tablets, with the exception of [redacted] propyl gallate and [redacted] hydroxypropyl methylcellulose. Both excipients have been used in other approved drug products in the FDA Inactive ingredient Guide (1/1996). Propyl gallate is used as intramuscular injection or topical drug at concentration of [redacted] and hydroxypropyl methyl-cellulose at doses up to of [redacted] mg in tablets. some clinical studies with the above combination drugs have been conducted under IND 52,791 and IND 65,066

7) Does the route of administration used in animal studies appear to be the same as the intended human exposure route? If not, has the sponsor submitted supportive data and/or an adequate scientific rationale to justify the alternative route?	Yes		The route of administration in a 14-month tox study conducted in dogs was oral, which is the intended route in humans
8) Has the proposed draft labeling been submitted? Are the appropriate sections for the product included and generally in accordance with 21 CFR 201.577? Is information available to express human dose multiples in either mg/m2 or comparative serum/plasma AUC levels?	Yes		Yes, the draft labeling submitted in general is similar to the approved ezetimibe label or simvastatin label, and data express human dose multiples in mg/m^2 or AUC levels.

ITEM	YES	NO	COMMENT
9) From a pharmacology/toxicology perspective, is this NDA fileable? If not, please state in item # 10 below why it is not.	Yes		

10) Reasons for refusal to file: Not applicable

APPEARS THIS WAY
ON ORIGINAL

Reviewing Pharmacologist: Indra Antonipillai, HFD-510

Supervisory Pharmacologist: Karen Davis-Bruno

File name: 21687-filing

APPEARS THIS WAY
ON ORIGINAL

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Indra Antonipillai
10/30/03 10:11:52 AM
PHARMACOLOGIST
This NDA application is filable
This application is filable

Karen Davis-Bruno
10/30/03 10:29:06 AM
PHARMACOLOGIST
filed NDA worksheet

10/31/03

Office of Clinical Pharmacology and Biopharmaceutics
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	21-687	Brand Name	Vytorin™
OCPB Division (I, II, III)	II	Generic Name	Ezetimibe/simvastatin combination
Medical Division	510	Drug Class	Lipid lowering
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	Primary hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH)
OCPB Team Leader	Hae-Young Ahn	Dosage Form	Tablet
		Dosing Regimen	Ezetimibe 10 mg and simvastatin 10 mg, 20 mg, 40 mg or 80 mg
Date of Submission	24 Sept. 03	Route of Administration	Oral
Estimated Due Date of OCPB Review	June 16, 2004	Sponsor	MSP Singapore, LLC
PDUFA Due Date	July 24, 2004	Priority Classification	standard
Division Due Date	June 24, 2004		

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments if any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				

alternate formulation as reference:				
Bioequivalence studies -				
traditional design; single / multi dose:	x	4		
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:	x			
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		4		

Filability and QBR comments		
	"X" if yes	**Comments**
Application filable ?	x	Reasons if the application is not filable (or an attachment if applicable) For example, is clinical formulation the same as the to-be-marketed one?
Comments sent to firm ?		The dissolution study was conducted in [redacted] with [redacted] using USP apparatus II (paddle) at [redacted] To optimize the dissolution method for quality control purpose as well as for granting biowaiver to strengths EZ10mg/Simva20 mg and EZ10 mg/Simva40 mg, the sponsor is recommended to investigate other two conditions such as at lower SLS level. The sponsor must submit dissolution profiles for all strength tablets from 3 batches under three different conditions.
QBR questions (key issues to be considered)	Bioequivalence between EZ 10-mg/Simva 10-mg combination tablet and individual tablets of EZ 10-mg tablets and Simva 10-mg coadministered Bioequivalence between EZ 10-mg/Simva 80-mg combination tablet and individual tablets of EZ 10-mg tablet sand Simva 80-mg coadministered	
Other comments or information not included above	Since the pivotal BE study is critical at bridging coadministration of individual tablets and combination tablet, it is desirable to conduct DSI inspection on pivotal study 039 **Clinical facilities:** **Site 001:** [redacted] **Site 00[redacted]** **Analytical sites:** Merck Research Laboratories, West Point, PA 19486 (Plasma samples were analyzed for SV and SVA) [redacted] (Plasma samples were analyzed for unconjugated and total ezetimibe)	
Primary reviewer Signature and Date		
Secondary reviewer Signature and Date		

MSP Singapore Company, LLC (MSP), a joint venture between Merck & Co., Inc. and Schering Corporation submitted an NDA for [redacted] (ezetimibe/simvastatin combination tablets). The sponsor proposed four combination tablet strengths, with each strength containing ezetimibe 10 mg and simvastatin 10, 20, 40, and 80 mg, for the treatment of hypercholesterolemia and homozygous familial hypercholesterolemia (HoFH).

Clinical pharmacology section contains the following studies:

Pivotal study:
Protocol 039: Multicenter Study: An Open-Label, Randomized, 2-Part, 2-Period, Crossover Study to Evaluate the Definitive Bioequivalence After Concomitant Administration of Single Doses of Ezetimibe and Simvastatin as Individual

Tablets and as the Final Market Image of the Ezetimibe/Simvastatin 10/10 and 10/80 Fixed-Dose Combination Tablets in Healthy Adult Subjects

Pilot studies:
1. Protocol 020
— Clinical Study Report: An Open-Label, Randomized, 4-Period Crossover Study to Evaluate the Relative Oral Bioavailability of Simvastatin Plasma HMG-CoA Reductase Inhibitory Activity and Total Ezetimibe Following Single Oral Doses of Simvastatin and Ezetimibe Administered to Young Healthy Subjects as a Probe Fixed-Dose Combination Tablet Versus Concomitantly as Separate Entities

2. Protocol 024
— Clinical Study Report. An Open-Label, Randomized, 2-Period Crossover Study to Evaluate the Relative Oral Bioavailability of Simvastatin Based on Plasma HMG-CoA Reductase Inhibitory Activity and Ezetimibe Based on Total Ezetimibe Concentrations, Following Single Oral Doses of Simvastatin and Ezetimibe Administered to Young Healthy Subjects as a Probe Fixed-Dose Combination Tablet Versus Concomitantly as Separate Entities

3. Protocol 028
— Clinical Study Report: An Open-Label, Randomized, 2-Period Crossover Study to Evaluate the Relative Oral Bioavailability of Total Ezetimibe and Simvastatin and Simvastatin Acid Plasma Concentrations Following Single Oral Doses of Simvastatin and Ezetimibe Administered to Young Healthy Subjects as a Probe Fixed-Dose Combination Tablet Versus Concomitantly as Separate Entities

Study results of Protocol 039 showed that the EZ 10-mg/Simva 10-mg combination tablet was bioequivalent to individual tablets of EZ 10-mg tablet sand Simva 10-mg coadministered in terms of AUClast and Cmax of EZ and AUClast and Cmax of simvastatin acid.
EZ 10 mg/Simva 80-mg combination tablet was bioequivalent to individual tablets of EZ 10-mg tablet sand Simva 80-mg coadministered in terms of AUClast and Cmax of EZ and AUClast and Cmax of simvastatin acid.

Individual raw data and pharmacokinetic results are included.

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/s/

Wei Qiu
10/28/03 02:49:11 PM
BIOPHARMACEUTICS

Hae-Young Ahn
10/31/03 10:17:23 AM
BIOPHARMACEUTICS

APPEARS THIS WAY
ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: May 25, 2004

TO: David Orloff, M.D., Director
Division of Metabolic and Endocrine Drug Products
HFD-510

VIA: Monika Johnson, Pharm. D., Regulatory Health Project Manager,
Division of Metabolic and Endocrine Drug Products
HFD-510

FROM: Jeanine Best, M.S.N., R.N., P.N.P.
Patient Product Information Specialist
Division of Surveillance, Research, and Communication Support
HFD-410

THROUGH: Gerald Dal Pan, M.D., M.H.S., Director
Division of Surveillance, Research, and Communication Support
HFD-410

SUBJECT: ODS/DSRCS Review of the Patient Labeling for Vytorin (ezetimibe/simvastatin) Tablets, NDA 21-687

The attached patient labeling (clean copies) represent the revised risk communication materials for Vytorin (ezetimibe/simvastatin) Tablets, NDA 21-687. It has been reviewed by our office and by DDMAC. We have simplified the wording, made it consistent with the PI, removed promotional language and other unnecessary information (the purpose of patient information leaflets is to enhance appropriate use and provide important risk information about medications), and put it in the format that we are recommending for all patient information. Our proposed changes are known through research and experience to improve risk communication to a broad audience of varying educational backgrounds. These revisions are based on draft labeling submitted by the sponsor on September 24, 2003. Patient information should always be consistent with the prescribing information. All future changes to the PI should also be reflected in the PPI.

Comments to the review division are bolded, underlined and italicized. We can provide marked-up and clean copies of the revised documents in Word if requested by the review division. Please call is if you have any questions

(D)

Number of Pages Redacted 4

❖❖❖

Draft Labeling
(not releasable

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

Jeanine Best
5/25/04 11:08:46 AM
DRUG SAFETY OFFICE REVIEWER

Gerald DalPan
5/25/04 03:29:03 PM
MEDICAL OFFICER

E

THIS SECTION WAS DETERMINED NOT TO BE RELEASABLE

9 pages

(F)

Number of Pages Redacted 76

❖❖❖

Draft Labeling
(not releasable

CONSULTATION RESPONSE

DIVISION OF MEDICATION ERRORS AND TECHNICAL SUPPORT
OFFICE OF DRUG SAFETY
(DMETS; HFD-420)

DATE RECEIVED: 09/15/03	**DESIRED COMPLETION DATE:** 11/15/03	**ODS CONSULT #:** 03-0260

TO: David G. Orloff, M.D.
Director, Division of Metabolic and Endocrine Drug Products
HFD-510

THROUGH: Valerie Jimenez
Project Manager
HFD-510

PRODUCT NAME:	**NDA:** Merck Research Laboratories
Vytorin™ (Ezetimibe and Simvastatin) Tablets 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg **NDA#:** 21-687 **(IND#:** 65,066)	

SAFETY EVALUATOR: Jinhee L. Jahng, Pharm.D.

RECOMMENDATIONS:

1 DMETS has no objections to the use of the proprietary name Vytorin™. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

2. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review in order to minimize potential errors with the use of this product.

3. DDMAC finds the proprietary name Vytorin™ acceptable from a promotional perspective.

Carol Holquist, R.Ph.
Deputy Director
Division of Medication Errors and Technical Support
Office of Drug Safety
Phone: (301) 827-3242 Fax: (301) 443-9664

Jerry Phillips, R.Ph.
Associate Director
Office of Drug Safety
Center for Drug Evaluation and Research
Food and Drug Administration

Division of Medication Errors and Technical Support (DMETS)
Office of Drug Safety
HFD-420; PKLN Rm. 6-34
Center for Drug Evaluation and Research

PROPRIETARY NAME REVIEW

DATE OF REVIEW: January 22, 2004

NDA#: 21-687 (IND#: 65,066)

NAME OF DRUG: Vytorin™ (Ezetimibe and Simvastatin Tablets)
10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg

NDA HOLDER: Merck Research Laboratories

I. INTRODUCTION:

This consult was written in response to a request from the Division of Metabolic and Endocrine Drug Products (HFD-510), for assessment of the proprietary name, "Vytorin", regarding potential name confusion with other proprietary or established drug names. The container labels, carton and insert labeling were provided for review and comment.

PRODUCT INFORMATION
Vytorin™ is a combination tablet which contains ezetimibe, a selective inhibitor of intestinal cholesterol and related phytosterol absorption, and simvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor. Vytorin™ is indicated for primary hypercholesterolemia and homozygous familial hypercholesterolemia. The dosage range is 10 mg/10 mg to 10 mg/80 mg daily. Vytorin™ is a tablet that will be available in four strengths: 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, and 10 mg/80 mg of ezetimibe and simvastatin respectively.

II. RISK ASSESSMENT:

The medication error staff of DMETS conducted a search of several standard published drug product reference texts[1,2] as well as several FDA databases[3] for existing drug names which sound-alike or look-alike to Vytorin to a degree where potential confusion between drug names could occur under the usual clinical practice settings. A search of the electronic online version of the U.S. Patent and Trademark Office's Text and Image Database was also conducted[4]. The Saegis[5] Pharma-In-Use database was searched for drug names with potential for confusion. An expert panel discussion was conducted

[1] MICROMEDEX Integrated Index, 2003, MICROMEDEX, Inc., 6200 South Syracuse Way, Suite 300, Englewood, Colorado 80111-4740, which includes all products/databases within ChemKnowledge, DrugKnowledge, and RegsKnowledge Systems.
[2] Facts and Comparisons, online version, Facts and Comparisons, St. Louis, MO.
[3] AMF Decision Support System [DSS], the Division of Medication Errors and Technical Support [DMETS] database of Proprietary name consultation requests, New Drug Approvals 98-03, and the electronic online version of the FDA Orange Book.
[4] WWW location http://www.uspto.gov/tmdb/index.html.
[5] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

to review all findings from the searches. In addition, DMETS conducted three prescription analysis studies consisting of two written prescription studies (inpatient and outpatient) and one verbal prescription study, involving health care practitioners within FDA. This exercise was conducted to simulate the prescription ordering process in order to evaluate potential errors in handwriting and verbal communication of the name.

A. EXPERT PANEL DISCUSSION (EPD)

An Expert Panel discussion was held by DMETS to gather professional opinions on the safety of the proprietary name Vytorin. Potential concerns regarding drug marketing and promotion related to the proposed name were also discussed. This group is composed of DMETS Medication Errors Prevention Staff and representation from the Division of Drug Marketing, Advertising, and Communications (DDMAC). The group relies on their clinical and other professional experiences and a number of standard references when making a decision on the acceptability of a proprietary name.

1. DDMAC finds the proprietary name Vytorin acceptable from a promotional perspective.

2. The Expert Panel identified six proprietary names that were thought to have the potential for confusion with Vytorin. These products are listed in Table 1 (see below), along with the dosage forms available and usual dosage.

Table 1: Potential Sound-Alike/Look-Alike Names Identified by DMETS Expert Panel

Product Name	Dosage form(s); Established name	Usual dose*	Other**
Vytorin	Ezetimibe and Simvastatin Tablets 10 mg/10 mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg	10 mg/10 mg to 10 mg/80 mg/day	
Vicoprin (not marketed)	Aspirin and Hydrocodone Bitartrate Tablets 500 mg/5mg	--	SA
Voltaren	Diclofenac Ophthalmic Solution 0.1% Diclofenac Delayed Release Tablets 25 mg, 50 mg, 75 mg	1 to 2 drops to affected eye(s) 4 times daily. 100 to 200 mg/day in divided doses.	SA
Vitron-C	Ferrous Fumarate and Ascorbic Acid Tablets 200 mg (66 mg iron)/125 mg	1 tablet daily.	LA
Zydone	Acetaminophen and Hydrocodone Tablets 400 mg/5 mg, 400 mg/7.5 mg, 400 mg/10 mg	1 tablet every 4 to 6 hours as needed. Max: 6 tablets/24 hours	LA
Vicodin	Acetaminophen and Hydrocodone Bitartrate Tablets 500 mg/5 mg	1 to 2 tablets every 4 to 6 hours as need. Max: 8 tablets/24 hours	SA/LA
Vytone	Hydrocortisone and Iodoquinol Cream 1%/1%	Apply 3 to 4 times daily to affected area.	SA/LA

*Frequently used, not all-inclusive.
**L/A (look-alike), S/A (sound-alike)

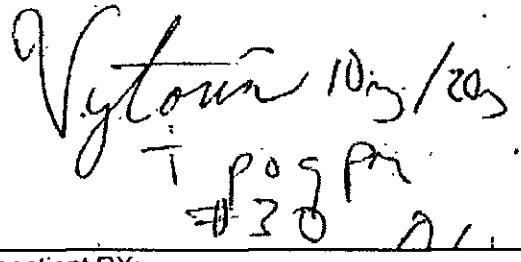
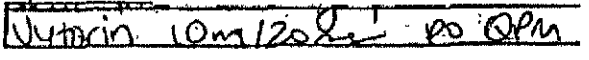
B. PHONETIC and ORTHOGRAPHIC COMPUTER ANALYSIS (POCA)

As part of the name similarity assessment, proposed names are evaluated via a phonetic/orthographic algorithm. The proposed proprietary name is converted into its phonemic representation before it runs through the phonetic algorithm. The phonetic search module returns a numeric score to the search engine based on the phonetic similarity to the input text. Likewise, an orthographic algorithm exists which operates in a similar fashion. All names considered to have significant phonetic or orthographic similarities to Vytorin were discussed by the Expert Panel (EPD).

C. PRESCRIPTION ANALYSIS STUDIES

1. Methodology:

Three separate studies were conducted within the Centers of the FDA for the proposed proprietary name to determine the degree of confusion of Vytorin with marketed U.S. drug names (proprietary and established) due to similarity in visual appearance with handwritten prescriptions or verbal pronunciation of the drug name. These studies employed a total of 127 health care professionals (pharmacists, physicians, and nurses). This exercise was conducted in an attempt to simulate the prescription ordering process. An inpatient order and outpatient prescriptions were written, each consisting of a combination of marketed and unapproved drug products and a prescription for Vytorin (see below). These prescriptions were optically scanned and one prescription was delivered to a random sample of the participating health professionals via e-mail. In addition, the outpatient orders were recorded on voice mail. The voice mail messages were then sent to a random sample of the participating health professionals for their interpretations and review. After receiving either the written or verbal prescription orders, the participants sent their interpretations of the orders via e-mail to the medication error staff.

HANDWRITTEN PRESCRIPTION	VERBAL PRESCRIPTION
Outpatient RX: 	Vytorin 10 mg/20 mg 1 tab po qPM #30
Inpatient RX: 	

2. Results:

None of the interpretations of the proposed name overlap, sound similar, or look similar to any currently marketed U.S. product. See appendix A for the complete listing of interpretations from the verbal and written studies.

D. SAFETY EVALUATOR RISK ASSESSMENT

In reviewing the proprietary name Vytorin, the primary concerns related to look-alike and sound-alike confusion with Vicoprin, Voltaren, Vitron-C, Zydone, Vicodin, and Vytone. Upon further review of the names gathered from EPD, the names Vicoprin and Vitron-C were not reviewed further due to a lack of convincing sound-alike/look-alike similarities with Vytorin in addition to numerous differentiating product characteristics such as the product strength, indication for use, and frequency of administration. Moreover, Vicoprin is no longer marketed in the United States and no longer appears in standard drug references (MICROMEDEX, Facts and Comparisons, FDA Orange Book, 2003 Drug Topics Red Book), minimizing the potential for confusion and error between Vicoprin and Vytorin. The products considered to have the greatest potential for name confusion with Vytorin are Voltaren, Zydone, Vicodin, and Vytone.

Additionally, DMETS conducted prescription studies to simulate the prescription ordering process. In this case, there was no confirmation that the proposed name could be confused with any of the aforementioned names. However, negative findings are not predicative as to what may occur once the drug is widely prescribed, as these studies have limitations primarily due to a small sample size. The majority of misinterpretations were misspelled/phonetic variations of the proposed name, Vytorin.

1. Voltaren and Vytorin were found to have sound-alike similarities. Voltaren (diclofenac) is a nonsteroidal antiinflammatory drug with antiinflammatory, analgesic, and antipyretic activity. Voltaren and Vytorin have three syllables and share similar sounds ("V" and "-taren" vs. "-torin"), however, the "Vol-" in Voltaren can be phonetically distinguished from the "Vy-" in Vytorin. Voltaren is readily available as an ophthalmic solution and tablet and can be dosed two to four times daily. Vytorin is available in tablet form, but it is given once daily. Although Voltaren and Vytorin share a common route of administration (oral) and dosage form (tablet), each product would need a specific dosage strength assigned when prescribed because of the multiple strengths that are available for each drug. None of the existing strengths overlap with one another (10 mg/10mg, 10 mg/20 mg, 10 mg/40 mg, 10 mg/80 mg vs. 0.1%, 25 mg, 50 mg, 75 mg) and Vytorin is comprised of two active ingredients whereas Voltaren has one active ingredient. DMETS believes differences in dosage strength, dosage schedule, and phonetic characteristics minimize the likelihood for confusion between the two drug products.

2. Zydone and Vytorin may look similar when scripted. Zydone (hydrocodone bitartrate and acetaminophen tablets) is an opioid analgesic and antitussive indicated for the relief of moderate to moderately severe pain. The "Z-" in Zydone resembles the "V-" in Vytorin, as do the last letters of each name "-ydon-" vs. "-ytori-" and "-e" vs. "-n" (see page 6). However, the positioning of these letters in their respective names differentiates one name from one the other. Zydone is typically administered 4 to 6 times daily as needed and often used for acute conditions, whereas Vytorin is given once daily for long term maintenance of hypercholesterolemia. Additionally, the Saegis[6] Pharma-In-Use database indicates that 2003 sales usage is low. They share a dosage strength that has the potential for confusion (400 mg/10 mg vs. 10 mg/40 mg), but their differences outweigh the

[6] Data provided by Thomson & Thomson's SAEGIS ™ Online Service, available at www.thomson-thomson.com

similarities and DMETS believes that the potential for confusion between Zydone and Vytorin is minimized because of the aforementioned product differences.

Zydone Vytorin

3. Vicodin and Vytorin were identified as having sound-alike and look-alike potential. Vicodin is a combination analgesic agent indicated for the relief of moderate to moderately severe pain. It is comprised of acetaminophen (a peripherally-acting analgesic) and hydrocodone (a centrally-acting, semi-synthetic narcotic analgesic). Both Vicodin and Vytorin have seven letters, sharing a number of overlapping letters (see below) in addition to similar sounds ("Vy-" vs. "Vi-" and "-in"). The letters "-rin" can resemble "-din" If the upstroke of the "-d-" in Vicodin is not written prominently. The products will most likely have a similar prescriber population, however, Vicodin is typically administered 4 to 6 times daily as needed and often used for acute conditions, whereas Vytorin is given once daily for long term maintenance of hypercholesterolemia. Despite some similarities in orthographic and phonetic characteristics, the differences (strength, dose, and dosage schedule) minimize the likelihood for a dispensing error to occur.

Vytorin
Vicodin

VYTORIN
VICODIN

4. Vytone and Vytorin look similar when written and sound similar when pronounced. Vytone (iodoquinol/hydrocortisone) is an amebicide and corticosteroid combination used to treat skin redness and itching due to eczema or infection. Vytone and Vytorin have the potential to sound-alike because they share a similar prefix, "Vyto-" and the suffixes of each name can sound similar especially if all the syllables in Vytorin are not clearly enunciated. Vytorin could be misinterpreted as VY-TORN instead of VY-TOR-IN. In addition, Vytone and Vytorin have several overlapping letters in their respective names (see below). However, Vytone has six letters whereas Vytorin has seven letters. The likelihood for confusion between Vytone and Vytorin is further minimized because the products have a different route of administration (topical vs. oral), dosage strength, and dosage schedule (3-4 times daily vs. once daily). Vytone is available in one strength (1%/1%); Vytorin is available in multiple strengths. Because Vytorin is available in multiple strengths, a prescriber would likely specify the strength when writing or calling in a prescription, thus minimizing the potential for a dispensing error. Vytone and Vytorin have the potential for look-alike and sound-alike confusion, but the likelihood is minimized because of the differences mentioned above.

Vytone Vytorin

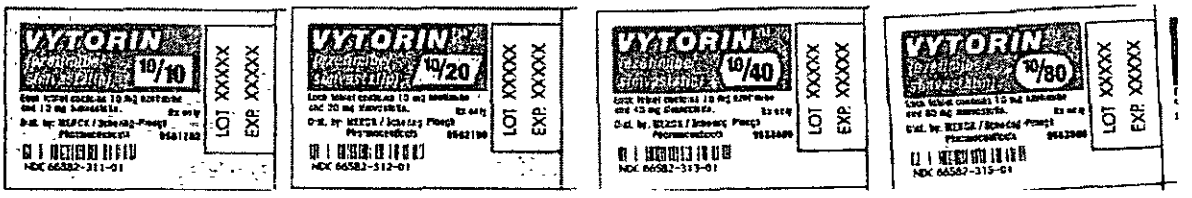
VYTONE
VYTORIN

III. LABELING, PACKAGING, AND SAFETY RELATED ISSUES:

In the review of the container labels, carton and insert labeling of Vytorin, DMETS has attempted to focus on safety issues relating to possible medication errors. We have identified several areas of possible improvement, which might minimize potential user error.

A. BLISTER LABEL

1. The sponsor has identified the varying strengths by using different geometric shapes to encapsulate the expression of strength. While the shapes are different, the colors and format of the labels remain the same. This method of differentiation increases the likelihood for a dispensing error to occur. The FDA has received several reports of potential and/or actual medication errors involving the packaging of other Merck Products (i.e. Zocor, Prinivil, Proscar, Pepcid, Vioxx, Singulair, Vasotec, Fosamax, and Emend), which differentiates its product strengths in the same fashion. DMETS recommends using contrasting color or some other means to appropriately distinguish one strength from the other.

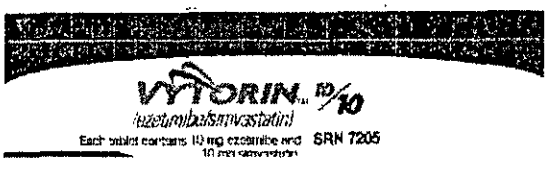


2. The product strength is present, but missing the unit designation (i.e. milligram). Please include the unit designation.

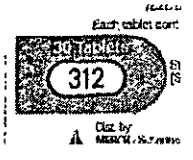
B. CONTAINER LABEL

1. See comment A2. In addition, the font colors and sizes for the product strength is different (see below). DMETS recommends differentiating the product strengths across the line but keeping each individual strength the same color.

2. Remove the graphic design located above the "-YT-" in VYTORIN (see below), as it may serve as a distraction, deemphasizing the prominence of the proprietary name.



3. The product code is more prominent than the net quantity (see below). DMETS recommends deemphasizing the prominence of this identifier as it may serve as a distraction.



4. We note the sponsor proposes to market this product as 30, 90, 500, and 1000 tablet bottles. We consider the 30 and 90 tablet bottles as unit of use bottles. Please ensure that the containers have a Child Resistant Closure (CRC) cap in order to be compliant with the Poison Prevention Act.

C. CARTON LABELING

1. See CONTAINER LABEL comments.

IV. RECOMMENDATIONS:

A. [redacted] Vytorin. This is considered a tentative decision and the firm should be notified that this name with its associated labels and labeling must be re-evaluated approximately 90 days prior to the expected approval of the NDA. A re-review of the name prior to NDA approval will rule out any objections based upon approvals of other proprietary or established names from the signature date of this document.

B. DMETS recommends implementation of the label and labeling revisions outlined in section III of this review that might lead to a safer use of the product. We would be willing to revisit these issues if the Division receives another draft of the labeling from the manufacturer.

C. [redacted]

DMETS would appreciate feedback of the final outcome of this consult. We would be willing to meet with the Division for further discussion, if needed. If you have further questions or need clarifications, please contact Sammie Beam, project manager, at 301-827-3242.

Jinhee L. Jahng, Pharm.D.
Safety Evaluator
Division of Medication Errors and Technical Support
Office of Drug Safety

Concur:

Alina Mahmud, R.Ph.
Team Leader
Division of Medication Errors and Technical Support
Office of Drug Safety

APPEARS THIS WAY
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Appendix A – DMETS Prescription Study Results

oice	Inpatient	Outpatient
Filtorez		
Fitoran	Vytorin	
Fitoren	Vytorin	Vytorin
Fitorin	Vytorin	Vytorin
Pfytorin	Vytorin	Vytorin
Phytoran	Vytoin	Vigtoun,
Phytoran	Vytorin	Vytorin
Phytoran	Vytarin	Vytorin
Phytorin	Vytovin	Vytorin
Phytorin	Vytorin	Vitorin
Phytorin	Vytorin	Vytoin
Vitoran	Vytorin	Vytorin
Vitoran	Vytorin	Vytorin
Vitoran	Vytorin	Vytorin
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Vitoren	vytorin	Vytorin
Vitorin	Vytorin	Vytorin
Vitorin	Vytorin	Vytorin
Vitorin	Vytorin	Vytorin
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Vitorin	Vytorin	Vytorin
Vitorin	Vytorin	Vytorin
Vitorin	Vytorin	Vytorin
Vitorin		Vytoun
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Vytorin		Vytorin
		Vytorin
		Vytorin

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/s/

Jinhee Jahng
3/19/04 04:09:28 PM
DRUG SAFETY OFFICE REVIEWER

Alina Mahmud
3/19/04 04:12:43 PM
DRUG SAFETY OFFICE REVIEWER

Carol Holquist
3/22/04 01:54:53 PM
DRUG SAFETY OFFICE REVIEWER

Jerry Phillips
3/22/04 02:58:02 PM
DRUG SAFETY OFFICE REVIEWER

3/3/03

EOPII

DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 65,066

Merck & Co., Inc.
Attention: Diane C. Louie, M.D., M.P.H.
Associate Director, Regulatory Affairs
P.O. Box 2000
Mail Drop: RY 33-720
Rahway, NJ 07065-0900

Dear Dr. Louie:

Please refer to the meeting between representatives of your firm and FDA on December 16, 2002. The purpose of the meeting was to discuss issues relating to the proposed Phase 3 development program that were not discussed at previous meetings.

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call me at (301) 827-6412.

Sincerely,

{See appended electronic signature page}

William C. Koch, R.Ph.
Regulatory Project Manager
Division of Metabolic
and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Enclosure

Meeting Date: December 16, 2002 Time: Location: PKLN 3rd floor "POTOMAC"

IND 65,066 MK-0653A (ezetimibe/simvastatin combination))

Type of Meeting: End-of-Phase 2

External Participant: MSP Singapore Company, LLC

Meeting Chair: David G. Orloff, M.D., Division Director

External Participant Lead: Robert Silverman, M.D., Ph.D., Senior Director, Regulatory Affairs

Meeting Recorder: William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

Robert J. Meyer, M.D., Director, Office of Drug Evaluation II
David G. Orloff, M.D., Division Director, Division of Metabolic and Endocrine Drug Products (DMEDP), ODEII
Mary H. Parks, M.D., Deputy Director, DMEDP
Jean W. Temeck, M.D., Clinical Reviewer, DMEDP
Hae-Young Ahn, Ph.D., Biopharmaceutics Team Leader, Division of Pharmaceutical Evaluation II, OCPB @ DMEDP
Wei Qiu, Ph.D., Biopharmaceutics Reviewer, Division of Pharmaceutical Evaluation II, OCPB @ DMEDP
Japobrata Choudhury, Ph.D., Statistical Reviewer, Division of Biometrics 2, OB @ DMEDP
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees and titles:

Robert Silverman, M.D., Ph.D., Senior Director, Regulatory Affairs-Domestic
Diane Louie, M.D., M.P.H., Associate Director Regulatory Affairs-Domestic
Susan Nolt, B.A., Coordinator, Regulatory Affairs
Thomas Hassall, M.S., Director, Regulatory Agency Relations
Michael Perelman, M.D., Director, Worldwide Regulatory Affairs
Beth DiDomenico, Ph.D., Manager, Worldwide Regulatory Affairs
John Paolini, M.D., Ph.D., Associate Director , Clinical Pharmacology
Gail Murphy, M.D., Senior Director, Clinical Pharmacology
Arthur Bergman, Ph.D., Senior Research Pharmacokineticist, Drug Metabolism
Thomas Musliner, M.D., Executive Director, Clinical Research
Enrico Veltri, M.D., Vice President, Clinical Research
George Lankas, Ph.D., Senior Director, Safety Assessment
Margaretann Halleck, Ph.D., Senior Principal Scientist, General Toxicology
Michael Stepanavage, M.S., Associate Director, Biostatistics and Research Decision Sciences
Deborah Shapiro, Dr. P.H., Senior Director, Biostatistics and Research Decision Sciences
Ramachandran Suresh, Ph.D., Associate Director, Statistics
Frances Pappas, M.S., Director, Clinical Trials Management
Yale Mitchell, M.D., Executive Director, Clinical Research

Meeting Objectives:

To discuss issues relating to the Phase 3 development program for the ezetimibe/simvastatin fixed-dose combination that were not discussed at previous meetings.

Discussion Points and Questions Submitted by Industry:

Non-Clinical Safety Assessment

1. Does the Agency agree that the non-clinical safety assessment program, including the relevant ezetimibe and simvastatin co-administration data, submitted to the approved Zetia (ezetimibe) Tablet application is sufficient to support the registration of the ezetimibe/simvastatin combination tablet?

The Division concurs with the proposal to rely on non-clinical safety data submitted to the approved Zetia application (NDA 21-445) is sufficient to support the registration of the combination tablet.

Clinical Pharmacology

2. Does the Agency agree that Clinical Pharmacology studies in addition to those summarized in tab 6 will not be required to support registration of the ezetimibe/simvastatin combination tablet?

The Division agrees that the clinical pharmacology studies summarized in Tab 6 of the pre-meeting package is sufficient to support the registration of the combination tablet.

Clinical Research

3. Does the Agency agree that the constituent studies of the proposed clinical program are adequate with regard to design, patient population, study duration, and endpoints to support the prototype **INDICATIONS AND USAGE** and **DOSAGE AND ADMINISTRATION** sections of the ezetimibe/simvastatin combination product label (tab 2).

The Division agrees with a reliance on the combination studies submitted to NDA 21-445 and also Protocol 039.

The Division recommends that the package insert for the ezetimibe/simvastatin product be a combination of both the simvastatin and the ezetimibe package inserts.

The sponsor asked if the Division agreed with a 10/10 start dose.

The Division agrees that the start dose should be the 10/10 strength.

4. MSP is conducting a randomized, double-blind study, Protocol 025, that compares the efficacy and safety of atorvastatin with ezetimibe/simvastatin combination therapy in approximately 700 patients with hypercholesterolemia. MSP believes that these data, in the context of the data from the 3 simvastatin factorial studies (005, P00680, 038) and the atorvastatin factorial study (P00692), are adequate to support the inclusion of the protocol 025 study description and its results in the **CLINICAL STUDIES** section of the ezetimibe/simvastatin combination product label. This approach follows the precedent of another statin, atorvastatin, whose current product label includes descriptions of a series of single comparator studies, each of atorvastatin versus a different statin, in the **CLINICAL STUDIES** section.

Does the Agency concur?

The sponsor added that now that the bioequivalence between the individual products and the combination tablet has been proven, [redacted]

The Division stated that the statisticians cannot commit to inclusion of data from the atorvastatin comparator study in the combination product label.

The Division further stated that comparator data may not be used for promotion as the data may be misleading.

Statistics

5. Based on the recent discussions with the FDA on the ezetimibe NDA 21-445 label, MSP proposes the following approach regarding multiplicity adjustments for key secondary endpoints in the ezetimibe/simvastatin combination NDA. First, we will examine the primary endpoint of LDL-C. If, and only if, a significant differenc e between pooled treatment groups is found for LDL-C (at $\alpha = 0.05$), then the key secondary endpoints of total-C, Apo B, triglycerides, and HDL-C will be evaluated. The Hochberg procedure with an overall $\alpha = 0.05$ will be used to control for multiplicity for these key secondary endpoints. For other supportive endpoints, there will be no further adjustment for multiplicity (i.e., we will test each at $\alpha = 0.05$, two-tailed). MSP believes that this approach will allow citation in the ezetimibe/simvastatin combination product label of relevant findings for the primary and key secondary endpoints. Does the Agency concur?

The Division agrees with the Hochberg procedure for secondary endpoints. However, for each and every hypothesis that may be tested, either a fixed-sequence or a multiple comparison adjustment method for other multiplicities has to be pre-specified.

Data Pooling

6. MSP proposes to designate 4 pools of data that will be analyzed separately for presentation of safety information in the ezetimibe/simvastatin NDA Integrated Summary of Safety. Three of the 4 pools
will provide blinded safety data on ezetimibe and simvastatin using Merck data handling rules, adverse experience dictionaries, and reporting conventions. The safety data from the fourth pool, the long-term Open-Label Safety pool, will be provided using the Schering-Plough format to maintain consistency with previous reports of studies in this pool submitted in the ezetimibe NDA 21-445 and its 4- and 8-month SURs. Does the Agency concur?

The Division recommends the following additional groups be included for safety:
for LFTs: ≥ 5 X ULN and ≥ 10 X ULN
for CPK: ≥ 10 X ULN with or without symptoms,
≥ 10 X ULN with symptom and
≥ 20 X ULN

Case narratives should be included.

Common Technical Document

7. MSP plans to submit the combination NDA in 4Q03 in the Common Technical Document (CTD) format in conformance with the draft guidance: *Submitting Marketing Applications According to the ICH=-CTD Format- General Considerations.* We anticipate cross-referencing to the respective ezetimibe and simvastatin NDAs in the ezetimibe/simvastatin combination NDA. MSP believes that because the ezetimibe and simvastatin NDAs were submitted prior to the implementation of the CTD, it is not necessary to reformat cross-referenced sections to conform to the CTD standard. Does the Agency concur?

The Division agrees that reformatting cross-referenced sections to conform to CTD standards is not necessary.

Cross-referencing

8. MSP anticipates submitting the ezetimibe/simvastatin combination NDA approximately one year after approval of the ezetimibe NDA 21-445. MSP, therefore, proposes to provide in the combination NDA only synopses of those studies that are cross-referenced to the ezetimibe NDA. Does the Agency concur?

The Division agrees with this proposal for providing synopses of cross-referenced studies.

Pediatric Use Information

9. Does the Agency agree that a waiver of pediatric studies for the ezetimibe/simvastatin combination NDA would be appropriate because the Proposed Pediatric Study submitted September 26, 2001, to the ezetimibe NDA 21-445 evaluates the safety and efficacy of ezetimibe and simvastatin co-administration?

The Division agrees with the waiver of pediatric studies for this combination.

The Division recommended that for Protocol 039 the bioequivalence data for both dosages of the combination be presented compared to the co-administration studies submitted to NDA 21-445 using the unconjugated ezetimibe.

Exploratory Issues: Biomarkers, Surrogate Endpoints and Clinical Outcomes Trials

10. MSP is considering clinical protocol concepts designed to explore the impact of the ezetimibe/simvastatin combination on important cardiovascular outcomes. The approaches include biomarkers beyond those already examined in the development program (e.g., additional lipoprotein species), vascular imaging techniques (e.g., IVUS and IMT), and clinical events (e.g., MI, stroke, etc.). MSP would welcome a discussion of the agency's current perspectives on the utility and general study design features of these approaches.

    The Division did not discuss clinical development programs relying on biomarkers and surrogate markers. Currently there are no guidelines issued and it was recommended that a separate meeting be held after the sponsor submitted a clinical proposal.

Unresolved or Issues Requiring Further Discussion:

The sponsor requested that the proposed NDA be accepted for filing with 9 months of stability data and a commitment to submit the 12-month data within 4 months of the original submission.

Action Items:

- None

Post-meeting Activity:

The Division accepts the sponsor's proposal to submit 9 months of stability data with the original NDA submission along with their commitment to submit the full 12 months of stability data within 4 months of the original submission with the understanding that 12 months of stability data would qualify the drug product for an 18-month expiry. Further stability data could be submitted as a supplement post-approval.

{See appended electronic signature page}

Prepared by: _____, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

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Concurrence: _____, Meeting Chair
David G. Orloff, M.D. date
Director

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/s/

David Orloff
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/s/

William Koch
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2/11/03

Meeting Date: November 14, 2002 Time: 03:00 PM Location: PKLN "POTOMAC"

IND 65,066	MK-0653A (ezetimibe/simvastatin combination) Tablets
Type of Meeting:	Face-to-Face Guidance
External Participant:	MSP Singapore company, LLC
Meeting Chair:	David G. Orloff, M.D., Director
External Participant Lead:	Robert Silverman, M.D., Ph.D., Senior Director, Regulatory Affairs - Domestic
Meeting Recorder:	William C. Koch, R.Ph., Regulatory Project Manager

FDA Attendees and titles:

David G. Orloff, M.D., Director, (DMEDP), ODEII
Mary H. Parks, M.D., Deputy Director, DMEDP
Jean W. Temeck, M.D., Clinical Reviewer, DMEDP
Todd Sahlroot, Ph.D., Team Leader, Division of Biometrics 2, OB @ DMEDP
Japobrata Choudhury, Ph.D., Statistical Reviewer, Division of Biometrics 2, OB @ DMEDP
Enid M. Galliers, Chief, Project Management Staff, DMEDP
William C. Koch, R.Ph., Regulatory Project Manager

External participant Attendees and titles:

Merck & Co, Inc.

Jonathan Tobert, M.D., Ph.D., Executive Director, Scientific Staff, Clinical Research
Thomas Musliner, M.D., Executive Director, Clinical Research
Michael Stepanavage, M.S., Associate Director, Biostatistics and Research Decision Sciences
Deborah Shapiro, Dr.P.H., Senior Director, Biostatistics and Research Decision Sciences
Linda Hostelley, B.S., Executive Director, Adverse Experience Reporting Worldwide, Worldwide Product Safety and Epidemiology
Thomas Hassail, M.S., Director, Regulatory Agency Relations
Susan Nolt, B.A., Senior Regulatory Coordinator, Regulatory Affairs
Diane Louie, M.D., M.P.H., Associate Director, Regulatory Affairs Domestic
Robert Silverman, M.D., Ph.D., Senior Director, Regulatory Affairs - Domestic

Schering Corp.

John Strony, M.D., Senior Director, Cardiovascular
Enrico Veltri, M.D. Vice President, Clinical Research
Michael Perelman, M.D., Director, Worldwide Regulatory Affairs

University of Oxford

Colin Baigent, B.M., B.Ch., M.Sc., Reader in Clinical Epidemiology, HARP Study Coordinator
Martin Landray, M.B., Ch.B., Ph.D., MRCP, Senior Research Fellow, HARP Clinical Coordinator
Rory Collins, M.B., B.S., M.Sc., Professor of Medicine and Epidemiology, Chair, HARP Steering Committee

University of Minnesota

Bert Kasiske, M.D., FACP, Professor of Medicine, Director, Division of Nephrology, Hennepin County Medical Center

Meeting Objectives:

To discuss the proposed clinical outcomes trial designated "Heart and Renal Protection" (HARP) study.

Discussion Points and Questions Submitted by Industry:

The Division asked about adverse event reporting for the study.

The sponsor replied that at each scheduled visit all serious adverse events and all non-serious adverse events involving muscle and liver would be reported.

The Division asked for the sponsor's definition of hepatitis.

The sponsor replied that liver transaminase elevations of all etiologies which require intervention would be considered to be hepatitis for purposes of this study.

The Division asked at what point in the study could the steering committee stop monitoring for CK levels.

The sponsor replied that the steering committee could, after consultation with the investigators, stop CK monitoring after one year in the absence of clinical or laboratory signals.

The Division requested that if the safety monitoring is stopped by the steering committee the rationale for stopping be submitted to the application and concurrence be obtained from the Agency before this policy be implemented.

The Division asked if there would be a full review of adverse events at any point.

The sponsor replied that a full review of adverse events would be conducted at each study visit.

The Division expressed concern regarding the potential occurrence of CNS disturbances (i.e., confusion, memory loss, etc.) secondary to drastic LDL-C reductions.

The sponsor stated that based on data obtained from the Heart Protection Study there was no evidence of CNS adverse events from lowering LDL-C.

The Division requested the sponsor's definition of serious adverse event and adverse events that would discontinue patients from the study.

The sponsor stated the a CPK elevation above 5 x ULN would trigger an early patient recall. The algorithm for CPK elevations is included in the protocol.

The Division recommended that the criteria for study drug discontinuation based on CK and LFTs should be consistent with the definition used in the Zetia NDA application.

The Division asked why the lipid-altering effects of treatment will be measured in all patients at the midpoint of the study and only in 10% of the patients at endpoint.

The sponsor explained that the goal was to arrive at an average over the entire length of the study.

The Division asked why the simvastatin-only arm of the study extended only to one year.

The sponsor replied that the number of patients in the simvastatin-only arm was not powered for assessing efficacy.

The Division asked if the covariates would be stratified.

The sponsor stated that a minimized randomization (Friedman-White) program would be used.

1. Oxford and MSP believe that the proposed HARP study is adequate with regard to the following aspects to support the addition of the prototype indications and usage language to the ezetimibe/simvastatin combination product label:

- Design – Randomized, double blind, placebo-controlled
- Patient population – Patients with chronic kidney disease
- Sample size - ~8000 patients in the ezetimibe/simvastatin combination versus placebo in the primary comparison (Arm 2 vs. Arm 1)
- Duration- At least 4 years of treatment
- Endpoints – Primary study outcome comparison to support the indications is of major vascular events in the ezetimibe/simvastatin combination versus placebo grouops (Arm 2 vs. Arm 1)

‹ Does the Agency concur?

The Division stated the HARP data would have to be reviewed before a discussion about indications could occur. The Division would approve only the individual components of the indication for the **INDICATIONS AND USAGE** section of the package insert that reached statistical significance. The Division stated that the results of this study could not be extrapolated to the general population at risk for coronary heart disease.

The Division reminded the sponsor that the multiple comparisons adjustment method for the secondary endpoints must be pre-specified or the Rule of Bonferroni will be used for the analysis.

The sponsor stated that a detailed statistical plan would be submitted to the application.

The Division stated that simvastatin 20 mg / ezetimibe 10 mg would need to be specified in the **DOSAGE AND ADMINISTRATION** section of the package insert for this patient population because this was the dose used in the study.

2. Oxford and MSP believe that the design of Arm 3 is adequate to identify adverse effects attributable to simvastatin 20 mg (through a comparison of simvastatin alone [Arm 3] versus placebo [Arm 1]) or to ezetimibe (through a comparison of ezetimibe/simvastatin combination [Arm 2] versus simvastatin alone [Arm 3]) in patients with chronic kidney disease. Does the Agency concur?

   The Division agrees that this rationale is appropriate.

3. Oxford and MSP believe that the primary, secondary and tertiary assessments, as summarized above and detailed in the draft HARP protocol, Sections 2.3.2 – 2.3.4 are appropriate. Does the Agency concur?

   The Division agrees with the plan.

   The Division asked why secondary endpoints will be assessed in all 9000 patients instead of the 8000 patients to be used in the primary analysis. The Division's preference is to conduct at least an alternative analysis excluding Arm #3 patients

   The sponsor stated that they will test for homogeneity between the 8000 and 1000 patient groups before combining the groups. This assessment in all patients will give greater power to compare the efficacy of the combination versus placebo.

   The Division stated that this trial has the potential to demonstrate the efficacy and safety of simvastatin/ezetimibe combination in this population, but without either an ezetimibe alone treatment arm or a simvastatin treatment arm out to 4 years, the contribution of the individual study drugs to the clinical outcome at study end cannot be determined.

4. The proposed HARP study has been designed in the model of a "large simple" clinical outcomes trial. Oxford and MSP believe that the procedure for monitoring and reporting adverse events, as outlined in Sections 2.5.2 and 3.6 of the draft HARP protocol, which includes restricting the reporting of non-serious adverse events to unexplained muscle pain or weakness, fulfills the requirements of the Agency for assessing the safety of the ezetimibe/simvastatin combination. Does the Agency Concur?

The Division agrees with this plan, but wants the plan for the full review of systems submitted to the application. Also, the Division asked that if the decision is made to discontinue CK monitoring at one year, the rationale be submitted to the Division in advance of such action.

Unresolved or Issues Requiring Further Discussion:

- None

Action Items:

The sponsor will submit a detailed statistical plan to the new IND.

The sponsor will submit a plan for a full review of systems to the IND.

Post-meeting Activity:

On November 15, 2002, the Division requested that a description of the randomization procedure for the HARP Trial be submitted to the IND.

On November 18, 2002, the Division requested a copy of the study CRF.

Prepared by: *{See appended electronic signature page}*
_____, Meeting Recorder
William C. Koch, R.Ph. date
Regulatory Project Manager

Concurrence: *{See appended electronic signature page}*
_____, Meeting Chair
David G. Orloff, M.D. date
Director

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/s/

David Orloff
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